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Original article

Characterization of Mood Instability through Bipolar Disorders: A cluster-analytic approach using weekly prospective life-chart methodology

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ABSTRACT

BackgroundThe aim of this study was to characterize mood instability (MI) in Bipolar Disorder (BD) and to investigate potential differences between subtype I and II.

MethodsLife-charts from weekly mood ratings of 90 patients were used to compute: weeks spent with symptoms, number of episodes, and MI. Regression analyses were conducted to assess the relationship between BD subtype and MI adjusting by all potential confounding factors. Hierarchical cluster analysis was performed to determine the appropriate number of clusters that described the data and to assign subjects to a specific cluster based on their MI. We then compared clusters on clinical and psychosocial outcomes.

ResultsMedian follow-up was 5 years (IQR: 3.6–7.9). Patients spent 15.2%, 5%, and 3% of follow-up with depressive, manic, and mixed symptoms, respectively. BD type II presented higher MI (β = 1.83, 95% CI: 0.66–3.00) and subsydromal symptoms than BD type I patients. No differences in functioning or recurrences were found between subtypes. Differences in MI between the two clusters mimicked those between type I and II but enhanced (β = 3.86, 95%CI -4.72, -2.66). High MI (n = 43) patients presented poorer functioning and higher recurrences compared to Low MI patients (n = 43).

ConclusionBD type II presented higher MI and subsyndromal symptoms than BD type I patients. However, these differences did not translate into clinically relevant outcomes. A classification based on MI may provide useful clinical insights.

1. Introduction

Mood instability is a core feature of Bipolar Disorders (BD) but it is also present in most common psychiatric conditions (borderline personality disorder, unipolar depression, and psychotic disorders) [1]. Specifically in BD, there is an increasing amount of evidence on the fact that mood instability is associated with poorer functional outcomes [2,3], increased use of health-care systems [4], cardiometabolic risk [5], and suicidality [4]. In addition, although it has been traditionally reported that BD II is a condition characterized by a higher mood instability than BD type I [6–8], recent studies suggested that there were no differences in mood instability between those disorders [9–12] or even that depressive mood instability was higher on BD type II [13] or in BD type I [14].

However, research on mood instability in BD has been characterized by heterogeneity in measures employed to define it and other shortcomings. For instance, most of the research addressing mood instability in BD usually confounds this concept with that of affective instability (AI) (see [15] for a review) which refers to a shorter, labile, and frequent mood change that is frequently associated with psychosocial cues. Conversely, Mood Instability alludes to sustained, pervasive affecting tone lasting for days, weeks or months that could or not be associated with psychosocial cues [6,16].Mood instability in BD has been largely addressed by using AI instruments [6,17,18], such as the Affective Lability Scale (ALS) [19], the Temperament Evaluation of Memphis, Pisa, and San Diego Questionnaire (TEMPS) [20], or the Mood Lability Scale (MLS) [21]. Finally, most research conducted evaluating mood instability *per se* with proper instruments has prioritized the use of self-reported measures [10,12,14,22] or, in

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the case of employing an observer-oriented measure, shorter-term follow-up periods were employed [1,3]. Given this scenario, the above-stated conflicting findings regarding the differences in mood instability between BD I and BD II are difficult to appraise.

The aim of this study was to evaluate mood instability in BD during a long-term follow-up period employing clinician-rated measures, and to investigate if differences between type I and II regarding mood instability exist. Secondly, we aimed to explore whether finding homogeneous patient groups by using cluster analyses could prove to be more useful in describing clinical course and psychosocial functioning than current BD subtypification.

2. Methods

2.1. Sample selection

A consecutive sample of 90 BD patients from the outpatients' population of the Bipolar Disorder Program of Favaloro University was obtained. Patients were included if they met the following criteria: i) having Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) diagnoses of BD I or II; and ii) a period of follow-up of more than 36 consecutive months in our program. Exclusion criteria were: current substance abuse/dependence, mental retardation, neurological disease, or any unstable clinical condition (such as hypothyroidism) that could affect their clinical course. We initiated follow-up for included patients after they were euthymic (defined by Hamilton Depression Rating Scale [HDRS] < 4 and Young Mania Rating Scale [YMRS] < 4) for at least 8 weeks since baseline. Index week was defined as the first week in the life-chart after meeting inclusion criteria and the 8 weeks of continued euthymia.

2.2. Clinical and symptomatic assessment

Clinical outcomes such as prior mood episodes, hospitalizations, suicide attempts, and age at onset were assessed via direct interview and confirmed through family reports when available. To account for affective dysregulation, TEMPS cyclothymia sub-score was obtained.

After enrollment, weekly evaluation of mood symptoms was performed by a trained clinician using YMRS and HDRS and employing a mood-charting technique (Fig. 1). MI was assessed using Mood Instability Factor (MIF), a score previously developed and reported by our group [2] and replicated by others [10]. MIF was calculated as the Nº of mood changes/Nº of years of follow-up, 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 (Fig. 1). Subsyndromal symptoms (SD) was measured as the number of weeks with subsyndromal symptomatology from all polarities divided by length of follow-up. Finally, episodic density (ED) was calculated as the number of full-blown episodes divided by the length of follow-up. As shown in Supplementary Fig. A2, MIF, SD and ED are not correlated concepts. High inter-rater reliability was obtained for scores in YMRS (intraclass correlation coefficient [ICC = 0.96]) and HDRS [ICC = 0.95]).

Clinical interviews were performed on clinical basis (i.e., according to clinical status, or required by the patient due to life stressors) with a typical interval of 2 to 8 weeks. Patients were followed from index week until leaving the program, end of study period (31 December 2015), or hospitalization.

2.3. Functional and pharmacological assessment

Functional outcomes were evaluated by means of the Global Assessment of Functioning (GAF) (DSM-IV) using clinical criteria when patients were euthymic (HDRS < 4 and YMRS < 4). We employed the latest GAF measurement available in the patient's chart. Treating clinicians were asked to confirm this measurement to ensure that it properly reflected that patient's psychosocial functioning.

Exposure to antidepressants, mood stabilizers, and antipsychotics was assessed by means of the Clinical Scale of Intensity, Frequency, and Duration of Psychopharmacological Treatment (IFD). 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 treated naturalistically during follow-up and the exposure was recorded as the cumulative exposure during the entire follow-up period.

2.4. Statistical analysis

For the comparison between BD I and II, baseline differences between groups were examined with Student's *t*-test for continuous variables and Fisher's exact test for dichotomous ones. To estimate the association between mood instability and subtype of BD, we fitted a regression model using bipolar subtype and adjusting by age and gender which served as our foundation model for predicting mood instability. Age was modelled using higher

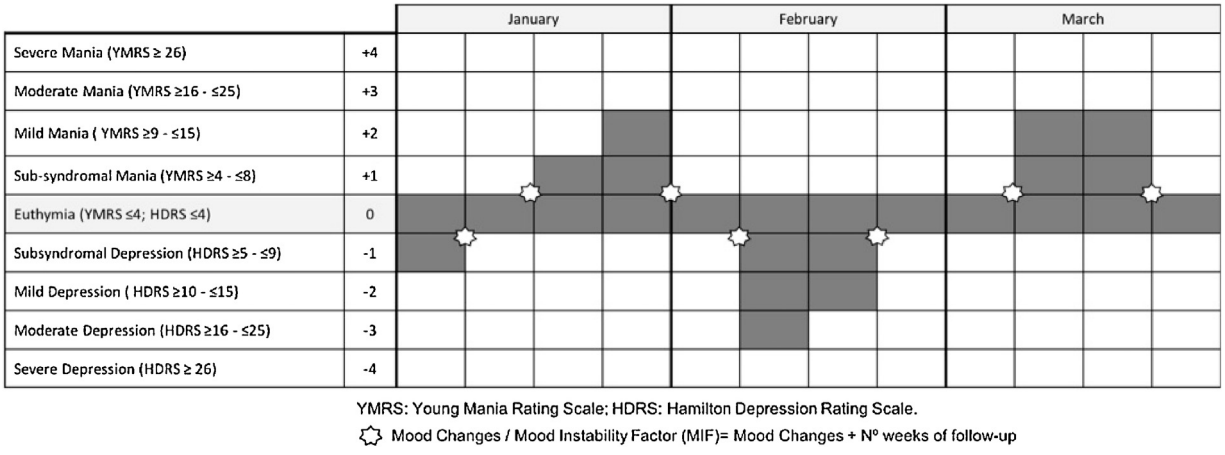

Fig. 1. Criteria for assigning a mood state and MIF in life-chart.

order polynomials to avoid linearity assumption. Candidate predictors for the multivariate analysis included demographical factors (education, employment status, functional status), clinical (psychotic symptoms, hospitalizations, prior episodes), and pharmacological exposure (cumulative exposure to antidepressants, antipsychotics and mood stabilizers). Predictors were screened for relationship with the outcome if univariate p values <.25 were identified when added to the foundation model. Predictors meeting this criterion were assessed using a stepwise backward analysis with $p < 0.05$ being the retention criteria. Age, gender, and bipolar subtype remained in the model despite their p values.

Secondly, in order to identify homogeneous subgroups in terms of mood instability, we performed a hierarchical cluster analysis (HCA). Similarity between cases was computed with the squared Euclidian distance and the Ward linkage was selected as the agglomeration procedure. Since the variables used to construct the clusters (Mood Instability Factor and Maximum Consecutive Weeks in Euthymia [MCWE]) were not standardized, we apply a pre-standardization procedure prior to clustering. The inspection of the dendogram was used as criterion to establish the appropriate number of clusters to retain. The data was considered small as to conduct a split-sample validation procedure.

The Hospital Ethics Committee approved the study and all subjects gave written informed consent for their participation after receiving a complete description of the study.

All statistical analyses were conducted using SPSS v21 and R statistical software version 3.4.1. All p values < 0.05 were considered as significant.

3. Results

A total of 90 patients were included. Mean age was 48.1 years (SD: 13.6) with a mean duration of illness of 22.2 years (SD: 10.6). Median follow-up was 5.0 years (IQR: 3.6–7.9). The cohort was comprised predominantly by women (70%) and the overall clinical course of the current sample was characterized by a predominant burden of depressive symptoms (15.2% of overall follow-up time), while a minor proportion of the follow-up was represented by hypo/manic (5.0%) and mixed (3.0%) symptoms. BD patients as a group experienced a mean of 3.6 mood changes per year (SD: 2.6, range: 0–15.3 changes per year) and the median maximum of continuous weeks spent in euthymia was 13.6 (range: 0–48 weeks).

BD type I and II were matched on most illness characteristics except for a greater number of prior hospitalizations on BD type I and a greater number of previous depressive episodes in BD type II (Table 1). In the univariate analysis, we found that patients with BD type I presented with an average of 3.0 mood changes per year while BD patients type II, 4.2 (t=-2.23, p = 0.02). Fig. 2 shows the probability density function of the MIF across bipolar subtypes. Further, patients with BD type II spent a significantly higher amount of the follow-up time with any depressive or hypo/manic

Table 1
Baseline characteristics and explanatory variables of BD type I and II.

Baseline characteristic	BD I (N = 48)	BD II (N = 42)	p value[1]
Demographical variables			
Age - years (mean, SD)	45.1 (11.9)	51.5 (14.7)	0.02
Male sex – (%)	37.5	21.4	0.09
Length of follow up (yr) (mean, SD)	6.2 (2.5)	5.8 (2.9)	0.48
Education (mean, SD)	14.6 (3.4)	14.6 (2.5)	0.96
Baseline clinical variables			
Psychotic symptoms – (%)	89.5	12.5	<0.001
Hospitalizations per yr (mean, SD)	0.4 (0.2)	0.1 (0.1)	<0.001
Duration of illness (mean, SD)	20.5 (9.9)	24.5 (11.3)	0.10
Previous hypo/manic episodes per yr (mean, SD)*	0.7 (0.6)	0.5 (0.4)	0.25
Previous depressive episodes per yr(mean, SD)*	0.5 (0.5)	1.0 (0.6)	<0.001
Suicide attempts (mean, SD)	0.3 (0.6)	0.5 (0.6)	0.42
Functional Outcomes			
GAF total score (mean, SD)	79.5 (11.4)	82.3 (9.9)	0.23
Follow-up Mood Instability Measures			
Mood Instability Factor (mean, SD)	3.0 (2.0)	4.2 (3.0)	0.03
Total number mood episodes per yr (mean, SD)	0.6 (0.6)	0.8 (0.6)	0.24
% time depressive symptoms (mean, SD)	10.5 (10.6)	20.5 (16.7)	0.01
% time hypo/manic symptoms (mean, SD)	7.1 (7.3)	2.3 (3.4)	0.01
% time mixed symptoms (mean, SD)	2.2 (3.4)	3.9 (6.3)	0.12
% time euthymia (mean, SD)	80.2 (14.3)	73.3 (18.1)	0.05
% of follow up with sub-syndromal depression (mean, SD)	7.0 (6.1)	12.4 (14.5)	0.03
% of follow up with sub-syndromal mania (mean, SD)	4.8 (5.2)	1.7 (2.8)	0.01
% of follow up with sub-syndromal mixed (mean, SD)	1.9 (3.1)	3.4 (5.6)	0.14
% of follow up with mild depressive symptoms (mean, SD)	2.7 (4.6)	5.8 (5.0)	0.01
% of follow up with mild hypomanic symptoms (mean, SD)	1.6 (2.0)	0.6 (0.9)	0.01
% of follow up with moderate depressive symptoms (mean, SD)	0.8 (1.9)	2.1 (3.6)	0.04
% of follow up with moderate manic symptoms (mean, SD)	0.7 (1.7)	0.1 (0.5)	0.04
% of follow up with moderate mixed symptoms (mean, SD)	0.2 (0.6)	0.3 (0.9)	0.63
% of follow up with severe depressive symptoms (mean, SD)	0.1 (0.4)	0.2 (0.6)	0.33
% of follow up with severe manic symptoms (mean, SD)	0.1 (0.4)	0.0 (0.0)	0.02
% of follow up with severe mixed symptoms (mean, SD)	0.0 (0.0)	0.2 (1.1)	0.24
Max. Weeks with continued euthymia (mean, SD)	18.9 (13.8)	14.7 (10.1)	0.11
Affective instability variables			
Cyclothymic TEMPS total score	7.3 (4.3)	10.5 (1.1)	0.06

Abbreviations: SD = Standard Deviation, yr = Years, GAF = Global Assessment of Functioning, BD = Bipolar Disorder.
[1] Two-sided p values. Mean values are compared with Student's *t*-test and proportions with X^2 test.

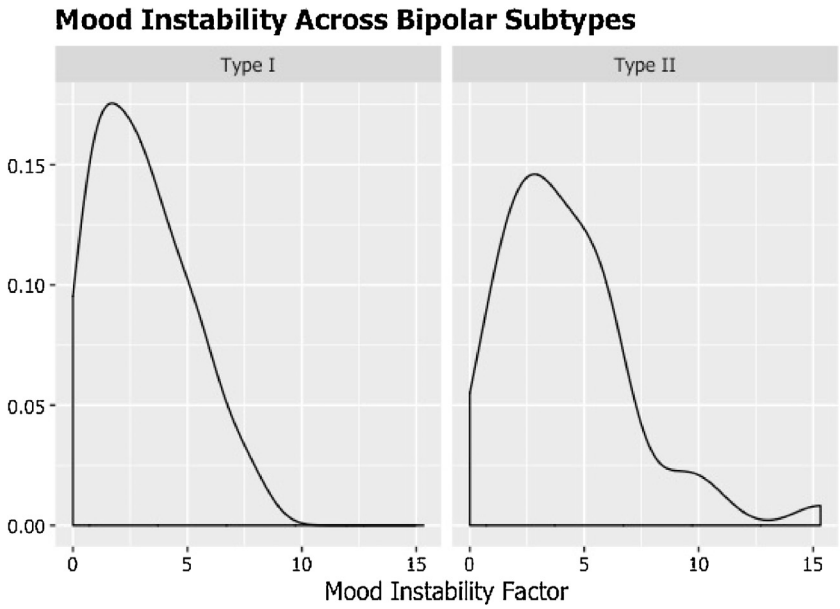

Fig. 2. Density plot for the distribution of mood instability across bipolar subtypes.

symptoms as compared with their type I counterparts (Table 1). Specifically, we found that these differences were mainly driven by subsyndromal symptomatology: while type I and type II patients did not differ in the number of full-blown episodes of any polarity during follow-up nor in the number of weeks spent with moderate or severe mood symptoms (with the exception of manic symptoms, by definition), they differed considerably in the amount of subsyndromal and mild symptoms (Table 1). Patients with BD type I and II did not differ significantly in the amount of exposure to mood stabilizers (t=-0.18, p = 0.85) but patients with BD type I had higher exposure to antipsychotic agents (t = 3.33, p = 0.001) and BD type II had higher exposure to antidepressants (t=-3.92, p < 0.001). Finally, a trend towards a higher cyclothymic temperament as measured by the TEMPS scale was observed in type II patients (Table 1).

In the regression analyses, we found a consistent pattern suggesting that patients with BD type II presented with higher mood instability than patients with BD type I (Table 2) as measured by the MIF. Bipolar subtype was significantly associated with mood instability in the crude, foundational, and final model. The final model adjusted R-square was 0.2932 which was improved from the crude and foundational parameters of 0.04 and 0.0432, respectively.

Specifically, we found that patients with BD type II have, on average, 1.83 more mood changes per year as compared to patients with BD type I, holding age, gender, global functioning, and number of previous episodes constant (Table 2). Despite this finding, we found no differences in psychosocial functioning nor number of recurrences during follow-up between patients with type II and type I (Table 1).

In the cluster analysis, we found that using the standardized MIF and the MCWE, a two-cluster solution was the optimal way of describing the data. The dendogram was visually inspected in order to select this optimal number of clusters and is shown in Supplementary eFig. 1. One cluster was comprised by patients with "High Mood Instability" (n = 43) and the other by patients with "Low Mood Instability" (n = 43). We found that both groups presented similar demographical variables, but patients with high mood instability had higher number of full-blown episodes during follow-up and a worse psychosocial functioning (Supplementary eTable 1). Interestingly, both clusters had similar proportion of BD type I and type II.

Finally, and as expected, clinical course was significantly different between the two clusters in most measures (Supplementary eTable 2). Broadly, patients belonging to the high instability cluster presented higher subsyndromal, and mild symptoms of all polarities in a similar way than the classification in type I and II but with greater effect sizes. In fact, after conditioning on age and gender, patients with high mood instability experienced, on average, 3.86 more mood changes than patients in the low mood instability cluster (β = 3.86, 95%CI -4.72 to -2.66).

Table 2
Crude and adjusted models exploring mood instability in BD type I vs type II.

	β Coefficient (BD subtype)	95% CI	P value
Crude Model	1.20	0.15 – 2.26	0.02
Foundational Model[&]	1.16	0.06 – 2.27	0.04
Final model[#]	1.83	0.66 – 3.00	<0.001

[&] Covariates included in the foundational model: age (as linear and quadratic terms) and gender.
[#] Covariates included in the final model: age (as linear and quadratic terms), gender, Global Functioning, number of previous manic episodes.

4. Discussion

The present study aimed at assessing Mood Instability across a sample of adults with BD during a median long-term follow-up period of 5 years using weekly prospective clinician-based measurements. The main finding of our study is that patients with BD type II had a significantly higher amount of subsyndromal and mild symptomatology of all polarities as compared to BD type I patients. This finding held even after controlling for potential confounding variables for this association. Further, we found that although patients with BD type II had higher mood instability than patients with BD type I, no differences in their psychosocial functioning or their rate of recurrences during follow-up could be observed. Finally, we found that a two-cluster approach properly described our data, with a cluster accounting for the group of patients with higher mood instability and another for the patients with lower mood instability (i.e., patients with no scarce inter-

episodic symptomatology). Interestingly, these clusters presented a significant association with psychosocial functioning and recurrences during follow-up.

Our results agree with initial clinical observations that suggested that BD type II patients had on average higher mood instability than BD type I [7,23,24]. We found that this association between mood instability and subtype of BD held even after accounting for potential confounding factors such as prior number of episodes, gender, and other clinical variables. Interestingly, the greater instability was shown to be at the expenses of a higher subsyndromal and mild symptomatology in agreement with clinical observations made by Judd et al. [25]. Previous studies reaching to conflicting results in regard to the mood instability in BD subtypes presented with methodological nuances such as self-reported mood status [3,10,12,14] or short-term follow-up periods [1,8,11]. Conversely, our results agree with a naturalistic study that employed a clinician-adjusted but self-reported measurement stating that BD type II patients presented with higher subsyndromal symptomatology burden than BD type I [26].

However, our results also showed that classifying BD in subtypes I and II was not effective in describing clinical relevant outcomes for these patients, namely, psychosocial functioning and number of recurrences during the follow-up period, in agreement with a longitudinal study looking at symptomatic burden of these conditions [25]. This may be due to the fact, that, although on average, BD type II patients had more mood changes per year than BD type I patients, this numeric difference may not have reached clinical relevance in order to impair psychosocial functioning in one group with respect to the other. As shown in Fig. 2, the density distribution of the MIF across bipolar subtypes is similar except that the distribution of type II BD is slightly flatter and presenting more outliers. This analysis supports visually the impression that this classification might not be distinguishing two truly distinct populations of BD patients in terms of this relevant clinical measure.

Conversely, by using cluster analyses, we aimed at discerning homogeneous subtypes with similar underlying mood instability by a method that is data-driven and that recognizes patterns in a heterogeneous group of patients. Latent class models, such as cluster analysis (CA), cluster individuals rather than variables into relatively homogeneous subgroups. As these types of models are designed to discover structure in the absence of pre-existing hypotheses about subtypes, they provide useful approaches for examining heterogeneity based on distinctions that are not known beforehand [27].

Clusters of BD patients according to their mood instability showed that the current classification in BD type I and II entails little information as to the degree of mood instability for a given patient. We found that 60% of patients in the low instability cluster had BD type I while 40% had BD type II, confirming our previous observation that this traditional categorization does not delineate two different clinical courses in terms of underlying mood instability. In fact, we observed that the two clusters clearly delineated two distinct groups of patients that distinguished themselves in terms of their subsyndromal and mild symptomatology in a much more meaningful way than type I and type II classification. Further, our results showed that low vs. high mood instability classification served in predicting psychosocial functioning as well as number of affective recurrences over follow-up better than traditional type I and type II classification. Since both associations have been well-described in literature, these results bring consistency to that previous work. Strejilevich et al. [2] using long-term follow-up periods and clinician-based measures showed the relationship between MI and psychosocial functioning and Judd et al. (2005) [25] showed how subsyndromal depressive symptomatology was linked to a significant functional impairment. Moreover, Stange et al. [28] in a randomized controlled trial from the STEP-BD study proved that mood instability was associated with clinical recurrences. These results may point that identifying patients regarding to their mood instability status may be useful as it has been recently proposed as a candidate biomarker that describes properly underlying BD pathology [29] based on the observations that it is present in high-risk of BD individuals [30], it predicts its onset [31,32], and it occurs during the prodrome and first-episodes of the disease [33].

Several limitations must be taken into consideration when interpreting the results of the present study. First, as our report relies on the use of clinician-based measurements of weekly mood ratings, the available data may be prone to measurement error as well as recall bias, as the interviewer might be assigning a particular mood status several weeks after. However, these biases might be non-differential in its nature and thus making our results, if anything, conservative [34]. Related to this, while this method might be readily available for clinicians to assess mood instability and relies on clinical observations rather than self-reporting, as opposed to electronic-based methods, it has the downside that it might not properly identify mood changes that occur within two interviews, or that occur within the same week. Although both methods have shown to be measuring the same phenomenon [35], it should be noted that inherent differences might exist. Second, given that allocation to pharmacological treatment was nonrandomized, the effect of varying treatments across subtypes could have confounded the results. Nevertheless, we found no evidence in this study suggesting that the association between mood instability and BD subtypes could be confounded by pharmacological treatment intensity. In fact, our stepwise backward selection of potential confounders did not select pharmacological intensity as a potential relevant variable for our final model. Third, since our study included only outpatients, generalization of these results to other populations may not be warranted. Fourth, since mood instability was defined on the basis of retrospective collection of mood symptoms in at least some cases, it remains plausible that patients reported mood symptoms that were more likely to affect future mood episodes, and/or functioning. Finally, since there might have been some degree of overlap between exposure ascertainment and the record clinical outcomes (i.e., the mood instability was measured during the same follow-up period as the number of recurrences) causal inferences from current results should be taken with caution.

In conclusion, patients with type II BD may experience a higher burden of subsyndromal and mild depressive and manic symptoms as well as mood changes during follow-up. However, the clinical impact of these differences appeared to be small. Classification of patients on the basis of their mood instability measured with standardized instruments appear to be relevant. Our results warrant further confirmation and external validation.

Source of funding

None.

Potential conflict of interests

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.eurpsy.2018.10.003.

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