Episodic density, subsyndromic symptoms, and mood instability in late-life bipolar disorders: A 5-year follow-up study

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Objectives: Characterization of clinical course in old age bipolar disorder (OABD) is scarce and based solely on episode density (ED). The aim of this study was to explore mood instability (MI) and subsyndromal symptomatology (SS) in a prospective cohort of OABD. Further, we contrasted these measures with a cohort of young age bipolar disorder (YABD).

Methods: Life charts from weekly mood ratings were used to compute the number of weeks spent with subsyndromal symptoms (SD), the ED, and the MI during follow-up for a cohort of OABD (N = 38) that excluded late onset BD. Linear and logistic regression models were fitted to compare the clinical course of OABD with a cohort of YABD (N = 52) and to explore the relationship between these measures and functional outcomes.

Results: Median follow-up was 5 years (IQR: 3.6-7.9). OABD (61.6 years, SD: 8.3) spent 15%, 6%, and 3% of their follow-up with depressive, manic, and mixed symptoms, respectively, and suffered 4.2 mood changes per year (SD: 2.6). No significant differences between OABD and YABD regarding ED or MI emerged in multivariate analysis, while a higher subsyndromal manic symptom burden was observed in OABD (β coefficient: 3.79, 95%CI: 0.4-7.2). Both SS and MI were associated with functional outcomes in OABD.

Conclusions: The course of illness throughout OABD was similar to the one observed in YABD except for a higher subsyndromal manic burden. This study extended the association of MI and SD with global functioning to the late-life BD.

KEYWORDS
bipolar disorder, late life, mood instability, older age bipolar disorder, psychosocial, subsyndromal

1 INTRODUCTION

Older age bipolar disorders (OABD) refers to the group of patients suffering from bipolar disorders (BD) having an age greater than 50.1 Although OABD are often understood as a special population, those with an early age at onset also represent a singular opportunity to investigate the long-term course of BD given that they have been suffering from a long-term disease and exposed to chronic treatment. However, this opportunity has been seldom seized. In fact, there is a dearth and inconsistency of data regarding clinical course throughout the old age1: while some longitudinal data have found an increase in the risk of recurrence in those with OABD after each new episode,2,3 other short-term study did not.4 Additionally, it was reported that recovery rates appear to remain relatively constant across affective
episodes in this population5 and that relapses leading to psychiatric admission seem to decrease with age, which may reflect a decrease in overall severity over time.6 More importantly, current data describing clinical course in OABD are fundamentally reliant on full-blown mood episodes (hypo/mania, depression, and mixed) along the disease evolution (episode density [ED]), leaving aside other clinical measures that have been shown to be relevant in predicting functional outcomes in young adults BD populations such as subsyndromal symptomatology (SS) or mood instability (MI).7,8

Subsyndromal symptomatology (SS)—that stands for the mood symptoms that have a level of intensity below the threshold required to diagnose a mood episode—dominates the clinical course of BD9 and is the best-documented independent predictors of functional outcomes in patients with these disorders (especially in the form of depressive symptoms).10,11 To assess the impact of SS along BD course, the term symptomatic density (SD) has been coined, which represents the percentage of time that BD patients experience SS along the course of their condition, or during a certain follow-up period. Additionally, MI refers to an emergent clinical concept that describes sustained and pervasive, syndromic or subsyndromic, fluctuations in mood and energy lasting for days, weeks, or months which are not necessarily associated with psychosocial outcomes. Mood instability is ubiquitous to many psychiatric conditions,12 but it is especially frequent in BD13 and has been described as an independent predictor of long-term functional outcomes in BD.7,8 Despite these findings, research on MI in BD has been characterized by heterogeneity in the measures employed to define them (see Renaud and Zaccia14 for a review) and other shortcomings, such as the use of self-reported measures15-18 or the use of short-term follow-up periods, which may affect their reliability.13,19,20 It is worth noting that MI is frequently mistaken with ”Affective Instability” which is a clinical concept that refers to a shorter, labile, and frequent mood changes normally associated with psychosocial events.14

To the best of our knowledge, no longitudinal studies have been carried out exploring SD and MI in OABD, nor the differences in these clinical course measures as compared with young adults with BD. Thus, the main aim of this work was to characterize the clinical profile of an OABD outpatient sample, measuring ED, SD, and MI over an extended follow-up period, and exploring the association between these variables and functional outcomes. Secondly, we used a sample of young age bipolar disorder (YABD) as an indirect control in order to detect possible changes in these variables due to illness evolution.

2 | METHODS

Two samples of patients were consecutively selected from the outpatients’ population of the Bipolar Disorder Program of Favaloro University: one of the older adults with BD (OABD), with an age of 50 or more, and other of young adults with BD (YABD)—with an age between 18 and 49 years. We used the age of 50 as the cut point following the recent ISBD OABD Task Force’s recommendations.1 Patients were included if they met the following criteria: (1) having

Key points

- Clinical course in older age bipolar disorder (OABD) is characterized based solely on mood episodes.
- This study provides description of mood instability and subsyndromal symptoms in OABD.
- Subsyndromal symptomatology and mood instability in OABD are largely similar to a cohort of young age bipolar disorder patients.
- Older adults might be prone to higher subsyndromal manic symptoms than their younger counterparts.

Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) diagnoses of BD I or II and (2) a period of follow-up of more than 36 consecutive months in our program. Exclusion criteria were (1) Minimental State Examination (MMSE) greater than 28; (2) presence of current unstable substance abuse/dependence that interferes with mood accountability; (3) mental retardation, neurological disease; or (4) any unstable clinical condition (such as hypothroidism) that could affect their clinical course. Finally, we excluded from the OABD sample those patients with late-onset BD (first manic episode after age 40) because they constitute a subgroup with a different clinical course and functional outcomes (for a review, see Sajatovic et al). 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.

2.1 | Clinical and functional assessment

Demographical and clinical information was obtained from patients’ life charts. Clinical course was assessed with a modified life charting technique rated by the treating psychiatrist on a weekly basis (Figure 1). Our mood chart is based on the NIMH life-charting method and anchored by scores from both the HDRS and the YMRS. High interrater reliability was obtained for scores in YMRS (interclass correlation coefficient [ICC = 0.96]) and HDRS (ICC = 0.95)21,22 and was developed for clinical purposes. Episodic density (ED) was defined as the number of full-blown episodes of each polarity (manic, depressive, and mixed) divided by the duration of the follow-up. SD was defined as the number of weeks spent with subsyndromal, mild, moderate, or severe symptoms of each polarity and also divided by the follow-up period. MI was assessed using mood instability factor (MIF), a score previously developed and reported by our group17 and replicated by others. 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 (Figure 1). Finally, we calculated the percentage of time spent under different episode severities according to mood chart scores and the maximum weeks spent continuously in euthymia (MSE).

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). Finally, occupational status was assessed as follows: (1) unemployed; (2) not working, receiving disability pension due to BD or other condition; (3) part-time employed; (4) student; and (5) full-time employed. This status was ascertained at the end of the follow-up, and clinicians were asked to confirm these measurements as to improve its reliability.

Clinical interviews were performed on clinical basis (ie, 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.

2.2 | Statistical analysis

Quantitative variables were presented as mean and standard deviation, or, in the case of noticeable skewness, as median and interquartile range. Baseline differences between YABD and OABD were assessed using X² test for categorical variables and T-test for continuous ones. To test the hypothesis of an increasing severity along the course of the disease, a multivariate linear regression was fit using MIF as the outcome variable and OABD as an indicator variable controlling for potential clinical course indexes, such as number of hospitalizations, psychotic symptoms, and prior to enrollment annual ED. Model assumptions were tested graphically (ie, by plotting the residuals against fitted values and by inspection of Q-Q plots of the residuals) and the presence of potential outliers was investigated. The association between MIF and functional outcomes differed in OABD and YABD, interaction terms were included in multivariate models when appropriate.

All descriptive statistical analyses were performed using STATA v.14.1 (StataCorp LP, College Station, Texas), and figures were constructed using R Statistical Software (version 3.4.4).

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.

3 | RESULTS

A total of 38 OABD and 52 YABD (38.3 ± 6.2 years old) were included in the present study. Median time of follow-up was 5 years (IQR: 3.6-7.9).

3.1 | Description of the OABD sample

OABD patients’ mean age was 61.6 years (standard deviation [SD]: 8.3, interquartile range [IQR]: 51-75), and their mean age at onset was 30.2 (SD: 7.9, IQR: 19-40); 62.5% had BD type II, and any history of suicide attempt was observed in 25% of the sample (Table 1). OABD patients experienced a mean of 0.24, 0.45, and 0.14 manic, depressive, and mixed episodes per year of follow-up, respectively. The ratio of manic/mixed episode to depressive ones was close to 1:1 (0.96, SD: 0.9). Furthermore, these patients spent 15% of their follow-up with any depressive, 6% with any manic, and 3% with any mixed symptomatology. Mean number of weeks continuously spent in euthymia (MSE) was 12.2 (SD: 8.5, range: 3.9-36.7). Finally, OABD experienced approximately four mood changes per year of follow-up (mean MIF: 4.2, SD: 2.6, range: 0.3-10.6).

3.2 | Comparison of the OABD and YABD samples

YABD main age was 38.3 ± 6.2 years old. The samples differed significantly in their duration of illness (16.0 ± 7.1 vs 30.7 ± 8.7 years; P < 0.01) but were overall balanced regarding most disease’s characteristics (Table 1). With the exception of subsyndromic manic symptoms, the numbers of weeks spent with any manic or depressive

![FIGURE 1](image-url)
TABLE 1 Baseline characteristics of old age bipolar disorder and young age bipolar disorder patients

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>YABD (N = 52)</th>
<th>OABD (N = 38)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographical variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age—years (mean, SD)</td>
<td>38.3 (6.2)</td>
<td>61.6 (8.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male sex—No. (%)</td>
<td>9 (17.3)</td>
<td>18 (47.4)</td>
<td>0.26</td>
</tr>
<tr>
<td>BD subtype (% BP I)—No. (%)</td>
<td>30 (57.7)</td>
<td>18 (47.4)</td>
<td>0.33</td>
</tr>
<tr>
<td>Education (mean, SD)</td>
<td>15.2 (2.6)</td>
<td>13.8 (3.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic symptoms—No. (%)</td>
<td>32 (61.5)</td>
<td>16 (42.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hospitalizations density (mean, SD)</td>
<td>0.1 (0.2)</td>
<td>0.1 (0.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Episode density (mean, SD)</td>
<td>1.3 (1.0)</td>
<td>2.2 (3.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Duration of illness (mean years, SD)</td>
<td>16.0 (7.1)</td>
<td>30.7 (8.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Suicide attempts density (mean, SD)</td>
<td>0.4 (0.6)</td>
<td>0.3 (0.6)</td>
<td>0.54</td>
</tr>
<tr>
<td>Diagnosis delay* (mean, SD)</td>
<td>6.0 (5.8)</td>
<td>15.5 (9.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Functional variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAF total score (mean, SD)</td>
<td>82.7 (11.6)</td>
<td>78.4 (9.3)</td>
<td>0.60</td>
</tr>
<tr>
<td>Full-time employment—No. (%)</td>
<td>16 (30.8)</td>
<td>8 (21.1)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Diagnosis delay was defined as age at diagnosis minus age at first mood episode.

Two-sided P values. Means are compared with Student’s T-test and proportions with the Fisher Exact’s test.

Abbreviation: BP-1, bipolar disorder type I.

symptoms during the follow-up did not differ between groups at any level of intensity (Figure 2). Furthermore, after controlling for indicators of disease severity, there were no statistically significant differences in the MIF between YABD and OABD during follow-up or in the number of weeks spent with subsyndromal symptoms of any polarity (Table 2). Furthermore, no differences in the maximum number of continuous weeks spent euthymic was observed (Figure 2).

Patients with OABD experienced a mean of 0.8 mood episodes per year of follow-up while patients with YABD, 0.6 (t = −1.60, P = 0.10). Mean depressive and manic episodes per year were 0.3 and 0.4 (t = −1.53, P = 0.13) and 0.2 and 0.2 (t = −0.75, P = 0.45) for OABD and YABD, respectively.

3.3 Relationship to functional outcomes

In the entire sample, MIF was significantly associated with functional outcomes measured by means of the GAF (β coefficient: −1.17, 95%CI −2.0 to −0.30, P value = 0.008) and by using a scale of employment status (β coefficient: −0.29, 95%CI −0.48 to −0.10, P value = 0.003). These measures suggest that a one-unit increase in MIF was associated with a 1.17 decrease in the GAF scale and with a 42% decrease in the probability of belonging to a higher employment category, controlling for indexes of disease severity (psychotic features, prior hospitalizations, and age at onset). Similarly, subsyndromal depressive symptoms were associated with a poorer psychosocial functioning after conditioning by proxies of disease severity (β coefficient: −0.28, 95%CI −0.48 to −0.07, P value = 0.006). Accordingly, maximum continuous weeks spent in euthymia was also significantly associated with functional status in the entire sample (β coefficient: 0.31, 95% CI: 0.13 to 0.48) indicating that per each continued week spent in euthymia, a 0.31 increase in GAF scores was observed.

Further, we explored whether this association was different between OABD and YABD by exploring interaction terms between MIF and this variable and keeping functional outcomes as the dependent variable. We found that the association between functional outcomes and MIF or MSE was not modified by OABD (P for the interaction terms: 0.108 and 0.152, respectively).

Finally, we found that subsyndromal manic symptoms did not predict functional outcomes nor in the total sample (β coefficient: −0.06, 95% CI −0.20 to 0.08, P value: 0.406) nor in the OABD cohort (β coefficient: −0.31, 95%CI −0.80 to 0.18, P value: 0.211).

4 DISCUSSION

The first aim of the present study was to describe ED, SS, and MI in a sample of OABD and its correlation with functional outcomes. We found that this sample of OABD experienced a burden of episodic and subsyndromic symptomatology that is widely similar to the one reported by prior research conducted on middle-life BD, supporting the claim of the recent Task Force on OABD that no differences in clinical presentation and course in OABD as compared with middle-life BD are expected. Additionally, we presented a description of MI in a late-life BD sample, finding similar values to the ones reported in younger BD patients. Second, we found that SD (especially subsyndromal depressive symptoms) and MI (as measured by the MIF) presented a strong and independent association with functional status in this sample of OABD. Thus, our results may help to extend this association previously reported in YABD to OABD patients, supporting the claim that SS and MI are essential clinical measures to define longitudinally these disorders. Moreover, a description of BD evolution only based in the number of episodes or episodic density is essentially incomplete, given that episodic density may mask underlying changes in SD and MI that have a significant impact on functional outcomes. In fact, for example, it is possible to observe an increase in episodic density concomitantly with a decrease in SD and MI or vice versa (see Strejilevich et al for a complete discussion).

Secondly, we have used a subset of YABD as a control group trying to capture possible modifications in ED, SS, and MI during the long-term BD evolution. Crude analyses of this comparison showed an increased MIF and subsyndromic manic symptoms in OABD compared with their young counterparts. After controlling by potential clinical course confounders (prior number of hospitalizations, presence of psychotic symptoms, and prior to enrollment annual ED), only an increase in manic subsyndromic symptoms remained significant. Overall, these
TABLE 2 Crude and adjusted linear regression model with mood parameters as outcome variables

<table>
<thead>
<tr>
<th>Condition (OABD vs YOBD)</th>
<th>Crude Coefficient (95% CI)</th>
<th>P Valuea</th>
<th>Adjusted Coefficient (95% CI)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIF</td>
<td>1.20 (0.06–2.18)</td>
<td>0.04*</td>
<td>0.46 (−0.56–1.47)</td>
<td>0.37</td>
</tr>
<tr>
<td>Subsyndromal mania</td>
<td>2.46 (0.62–4.31)</td>
<td>0.01*</td>
<td>3.79 (0.40–7.19)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Subsyndromal depressive</td>
<td>−0.59 (−5.33–4.15)</td>
<td>0.80</td>
<td>−2.26 (−7.40–2.88)</td>
<td>0.38</td>
</tr>
<tr>
<td>Mild mixed</td>
<td>−0.51 (−2.42–1.41)</td>
<td>0.60</td>
<td>−1.34 (−3.41–0.74)</td>
<td>0.20</td>
</tr>
<tr>
<td>Mild mania</td>
<td>0.38 (0.32–1.08)</td>
<td>0.29</td>
<td>0.34 (−0.37–1.05)</td>
<td>0.35</td>
</tr>
<tr>
<td>Mild depression</td>
<td>0.37 (−1.77–2.51)</td>
<td>0.73</td>
<td>−1.30 (−3.21–0.62)</td>
<td>0.18</td>
</tr>
<tr>
<td>Moderate depression</td>
<td>0.36 (−0.88–1.61)</td>
<td>0.57</td>
<td>−0.14 (−1.48–1.20)</td>
<td>0.84</td>
</tr>
<tr>
<td>Moderate mania</td>
<td>−0.36 (−0.91–0.19)</td>
<td>0.19</td>
<td>−0.45 (−1.02–0.12)</td>
<td>0.12</td>
</tr>
<tr>
<td>Moderate mixed</td>
<td>0.18 (−0.14–0.50)</td>
<td>0.26</td>
<td>0.13 (−0.21–0.47)</td>
<td>0.45</td>
</tr>
<tr>
<td>Severe mania</td>
<td>0.07 (−0.05–0.19)</td>
<td>0.24</td>
<td>0.08 (−0.05–0.21)</td>
<td>0.23</td>
</tr>
<tr>
<td>Severe depression</td>
<td>0.13 (−0.09–0.35)</td>
<td>0.23</td>
<td>0.09 (−0.14–0.32)</td>
<td>0.45</td>
</tr>
<tr>
<td>Severe mixed</td>
<td>−0.16 (−0.49–0.16)</td>
<td>0.31</td>
<td>−0.23 (−0.59–0.12)</td>
<td>0.20</td>
</tr>
<tr>
<td>Max weeks euthymia</td>
<td>−19.0 (−54.13–16.06)</td>
<td>0.28</td>
<td>−12.51 (−51.76–26.74)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Abbreviations: 95% CI, 95% confidence interval; max., maximum; MIF, mood instability factor; OABD, older age bipolar disorder; YABD, young age bipolar disorder.

*Significant at P < 0.05.

aUnivariate linear regression model.

bMultivariate linear model including previous hospitalization rate, psychotic symptoms, and prior episode density as confounders.
findings show that the burden of clinical morbidity experienced by BD patients as a group tends to be relatively stable over the long-term course of these conditions. The null finding of no differences in ED between the OABD and YABD samples agrees with a recent 3-year follow-up study\(^3\) but not with previous studies conducted using Denmark health care data.\(^3\) Two factors can explain these differences: first, we were able to perform a detailed assessment of the prior clinical course variables that we used to control for confounding and, second, that our sample included BD II patients as well as BD I patients, and also patients who did not present psychiatric hospitalizations, representing thus a more naturalistic sample. Finally, the finding that subsyndromal manic symptomatology is higher throughout OABD raises interesting hypotheses regarding its nature (ie, disinhibition due to advanced age, or early manifestation of mild cognitive impairment). However, the lack of a functional impairment associated with these symptoms challenges the real clinical impact of this finding, which warrant further research to disentangle.

Interestingly, these data also failed to show a progressive decrement of general symptomatology and MIF over the course of BD in patients continuously treated in a mood disorder clinic and following current international treatment guidelines. This finding should be taken with caution as it remains possible that OABD patients with remitting symptomatology were less represented in our included sample. However, further studies should inspect the degree of improvement achieved by current treatment strategies using MIF and SS measures as it might help set the expectations and achieve a realistic cost-effectiveness analysis, essential for any clinical decision-making process. Nevertheless, it should be noted that these data refer to BD as a group and therefore cannot rule out the possibility that specific subgroups in terms of general evolution and response to treatment might exist, as suggested by a number of previous reports in YABD\(^2,22-24\) and OABD.\(^4\)

Several limitations should be taken into account when interpreting the present results. First, our sample size might have precluded us from detecting existing differences between OABD and YABD populations. Second, the OABD group might be composed of patients with a more benign disease course—thus allowing them to continue in our cohort—hence, limiting generalizability of the present results. Third, measurement error in accounting for symptomatology in life charts—that was probably nondifferential in its nature—could be at least partly responsible for the null findings. Fourth, our results are dependent on our choice to define MI, namely, the MI factor. Although this measure has been validated by some research\(^1,2,24\) conducted by our group, further studies replicating these findings are warranted.

In summary, these data confirm the need to incorporate subsyndromatic symptoms and MI measurements in the design of longitudinal studies, in order to provide a complete map of clinical evolution of these chronic, heterogeneous, and disabling disorders. On the other hand, this study shows no evidence of a progressive increase in clinical morbidity along the course of BD. These data highlight how critically needed the description a proper model of long-term clinical evolution of BD is.

### 5 CONCLUSION

The course of illness throughout OABD was similar to the one observed in YABD except for a higher subsyndromal manic burden. This study extended the association of MI and SD with global functioning to the late-life BD and underlines the importance of including these measures to describe the clinical course of BD in late-life patients. Further research should focus on the ideal measure to capture MI in OABD and to corroborate these findings regarding an association between MI and functional outcomes.

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### CONFLICT OF INTEREST

None declared.

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### REFERENCES


