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Original article

A 12-month prospective study on the time to hospitalization and clinical management of a cohort of bipolar type I and schizoaffective bipolar patients

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ABSTRACT

Background: Schizoaffective disorder, bipolar type (SAD) and bipolar disorder I (BD) present a large clinical overlap. In a 1-year follow-up, we aimed to evaluate days to hospitalization (DTH) and predictors of relapse in a SAD-BD cohort of patients.
Methods: A 1–year, prospective, naturalistic cohort study considering DTH as primary outcome and incidence of direct and indirect measures of psychopathological compensation as secondary outcomes. Kaplan-Meyer survival analysis with Log-rank Mantel-Cox test compared BD/SAD subgroups as to DTH. After bivariate analyses, Cox regression was performed to assess covariates possibly associated with DTH in diagnostic subgroups.
Results: Of 836 screened patients, 437 were finally included (SAD = 105; BD = 332). Relapse rates in the SAD sample was n = 26 (24.8%) vs. n = 41 (12.3%) in the BD sample (p = 0.002). Mean ± SD DTH were 312.16 ± 10.6 (SAD) vs. 337.62 ± 4.4 (BD) days (p = 0.002). Patients with relapses showed more frequent suicide acts, violent behaviors, and changes in pharmacological treatments (all $p < 0.0005$) in comparison to patients without relapse. Patients without relapses had significantly higher mean number of treatments at T0 (p = 0.010). Cox regression model relating the association between diagnosis and DTH revealed that BD had higher rates of suicide attempts (HR = 13.0, 95%CI = 4.0–42.0, $p < 0.0005$), whereas SAD had higher rates of violent behavior during psychotic episodes (HR = 12.0, 95%CI = .3.3-43.5, $p > 0.0005$).
Conclusions: SAD patients relapse earlier with higher hospitalization rates and violent behavior during psychotic episodes whereas bipolar patients have more suicide attempts. Psychiatric/psychological follow-up visits may delay hospitalizations by closely monitoring symptoms of self- and hetero-aggression.

1. Introduction

Bipolar affective (BD) and schizoaffective (SAD) disorders are complex, severe conditions characterized by a high degree of clinical overlap during acute and cross-sectional evaluation, and a chronic, relapsing longitudinal course [1]. Together with

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schizophrenia, these conditions share high heritability estimates [2], substantial overlap with a high genetic correlation [3], and high relative risks of developing one of these conditions among relatives of both purely affective and psychotic patients [4].

Contrary to BD and schizophrenia, a controversial nosological discussion [5,6], criticism over its poor diagnostic reliability [7] and its clinical heterogeneity [8] have surrounded the SAD diagnosis since its appearance in psychiatric diagnostic classifications.

When studied in clinical settings, SAD has been generally considered with intermediate severity, between BD and schizophrenia [9], and its clinical management has suffered from an overall lack of population-specific research, being mostly grounded on extrapolations from BD or purely psychotic samples [10,11].

Despite an increase in the overall treatment options and optimistic results from randomized controlled trials, more than half of all BD patients relapse within 2 years, with possibility to experience at least 1 additional acute episode during their life time [12–14]. Similar data on SAD are scant, as fewer randomized controlled trials and naturalistic studies have been performed so far [15,16]. An indirect note for high relapse rates anyway is that SAD accounted for up to one-quarter of admissions to acute units in the past [17] and up to 31.3% in inpatients settings currently [18]. SAD and BD may seem indistinguishable in acute, cross-sectional clinical presentation. A longitudinal diagnostic evaluation especially aimed at the persistence and overall duration of affective and psychotic symptoms seems of paramount importance to better define the bipolar and schizoaffective populations [19], but, contrary to BD, clinical research on the course of illness of SAD is scant. Luckily, the latest international classification system introduced a more longitudinal evaluation of the time spent with purely psychotic or affective symptoms [20], with an improved reliability in SAD's diagnostic stability [21], but with unclear clinical implications.

Consequently, prospective, observational naturalistic studies are warranted and could clarify practical implication in distinguishing SAD bipolar from pure BD populations, and they might help filling the gap between the scant clinical trials and clinical practice in SAD. Comparison with BD would be specially needed to understand to which extent SAD may be reduced to a severe form of BD. For this reason, we decided to follow-up a cohort of patients followed-up in our tertiary care setting.

We hypothesized that relapsing patients would be more frequent among the SAD population, and that SAD patients would show a more severe clinical course, and a decreased tendency to psychopathological compensation. For this reason, we compared the clinical course of a cohort of BD and SAD patients followed-up during one year, considering time to hospitalization as a main outcome. We also considered direct (i.e. following hospitalizations, violent behaviors and suicidal acts), and indirect (i.e. type and number of treatments, and changes in treatments during the follow-up) measures of psychopathological compensation. Finally, we also evaluated possible hazards ratio associated with predictor variables in the BD and SAD diagnostic subgroups.

2. Methods

2.1. Study design and participants

In this prospective, naturalistic cohort study we chose *a priori* one year (referred to as *index* year, IY) in the life and course of illness of patients enrolled, assessed and treated in the Bipolar Disorders Unit of Barcelona, with the approval of the local ethics committees and in accordance with the ethical principles of the Declaration of Helsinki. [22].

2.2. Inclusion/Exclusion criteria

Patients were considered for inclusion only if their clinical history was electronically recorded. We considered an index year (IY) starting from the 1st of January 2015, to the 31th December 2015. Inclusion criteria were age older than 18 years, fulfilling diagnosis for BD type I or SAD according to DSM-IV-TR [23] and a follow-up during at least one year. Exclusion criteria were pregnancy or no availability of data during the IY (e.g. patients not resident in the catchment area that had a brief contact with our Unit).

2.3. Assessment

Basic demographic information (age, gender) were extracted from the electronic clinical history of each patient. Direct measures of psychopathological compensation were defined *a priori* as the presence of a new hospitalization, time to a new hospitalization, total number of hospitalizations, episode type of hospitalization (i.e. purely psychotic, nonpsychotic or psychotic manic, nonpsychotic or psychotic mixed, nonpsychotic or depressed episode), presence and number of suicidal attempts, presence and number of violent behaviors (physical, either towards objects or people), episode type of violent behaviors (psychotic, manic, depressive, mixed), and number of emergency attendances for acute symptoms not resulting in hospitalization, but not for other reasons such as prescription renewal.

Indirect, treatment-related measures of psychopathological compensation were defined *a priori* as number of "major treatment" (definition see below) at T0 (alone, with benzodiazepines, with other psychotropic medications), number of "major treatments" at T1 (alone, with benzodiazepines, with other psychotropic medications), total changes in "major treatments", total number and change of antipsychotic medication taken in 365 days, total number and change of mood-stabilizers taken in 365 days, total number and change of antidepressants taken in 365 days, beginning or discontinuation, or both beginning and discontinuation of long-acting treatment, and treatment with electroconvulsive therapy (ECT). "Major treatments" were defined as first- or second-line treatments for at least 1 phase among acute mania, acute depression, long-term treatment for BD and for SAD [24–26]. We decided to use the same definition of "major treatment" also for SAD patients due to the lack of clinical guidelines for SAD and the substantial overlap in the type of drugs used [11,27].

2.4. Statistical analyses

Kaplan-Meyer survival analysis with Log-rank Mantel-Cox test was used to compare diagnostic subgroups as to time to hospitalization, using the overall mean time to hospitalization as a threshold for event/censorship. Bivariate analyses were performed with Chi-square tests, independent-samples t-test, or Mann-Whitney U test (according to type of distribution of the variable). Cox regression (proportional hazard analysis) was performed in order to assess covariates possibly associated with time to hospitalization, and including statistically significant variables differentiating the 2 diagnostic subgroups. Statistical analyses were performed using the Statistical Package for Social Sciences (Statistical Package for Social Science-SPSS, 23.0 version for Windows Inc., Chicago, IL, USA). All p values were two-tailed and statistical significance was set at $p<0.05$.

3. Results

A complete flowchart showing the patients' selection process from computerized entries (visits) during IY to final sample included is presented in Fig. 1.

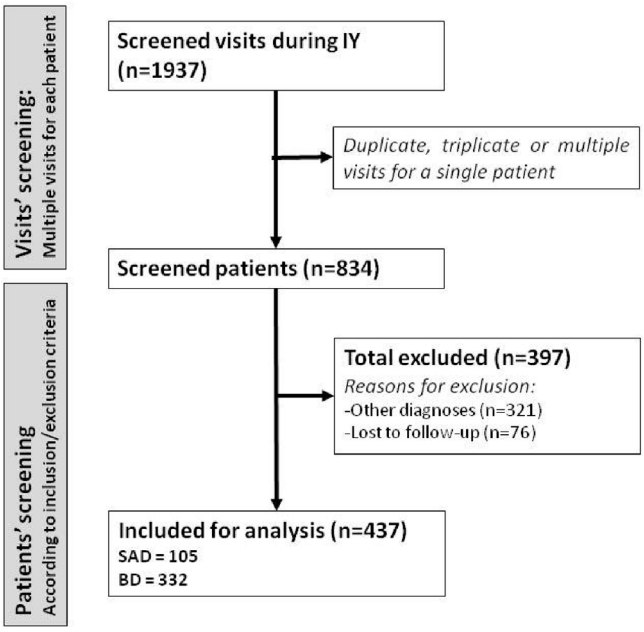

Fig. 1. Flowchart of included patients. All electronic visit entries scanned during Index Year were attributed to a pool of patients that underwent screening for inclusion or exclusion from the present study. **BD** = *Bipolar disorder, type I*; **IY** = *Index Year*; **SAD** = *Schizoaffective disorder, bipolar subtype*.

A total of 836 patients were screened for inclusion in the present study, of which 437 were finally included in the present study. Of those, 332 fulfilled a diagnosis for BD type I disorder, 105 for SAD, bipolar subtype. Baseline characteristics (sex and mean age) of the diagnostic subgroups were not statistically different (see Table 1).

3.1. Relapses and time to hospitalization

SAD patients relapsed with hospitalization statistically more frequently than BD patients SAD (n = 26/105, 24.8%) vs. BD (n = 41/332, 12.3%), $\chi^2 = 9.468$, p = 0.002). Mean time (±SD) to hospitalization was 312.2 (±10.6) days for SAD and 337.6 (±4.4) days for BD. These differences were statistically significant (Mantel Cox $\chi^2 = 9{,}421$, p = 0.002) (Fig. 2).

When relapsing patients were compared according to diagnostic subgroups, SAD patients showed significantly less (0, [0-0]) depressive episodes without psychotic symptoms than BD patients (0, [0–1], U = 390.000, p = 0.004), less changes in mood-stabilizers (SAD = 0, [0–1], BD = 0, [0–4], U = 281,500, p < 0.0001).

3.2. Direct measures of psychopathological compensation

3.2.1. All patients relapse versus non-relapse

All relapsing patients, both BD and SAD, had more emergency attendances and suffered from more frequent suicidal acts and violent behaviors than those without relapses (all <0.0005). A summary of the differences between patients with or without relapses in direct measures of psychopathological compensation is presented in Table 2.

Table 1
Baseline demographic characteristics in diagnostic subgroups.

Variables	BD (n = 332)		SAD (n = 105)		test	p
Female sex (n)	182	54.8%	58	55.2%	0.006[1]	0.940
Age (years)	52.89	±33.09	51.17	±39.32	0.443[2]	0.658

Notes: BD = *Bipolar Disorder*; **SAD** = *Schizoaffective Disorder*; **SD** = *Standard Deviation*.
Type of statistical test: **1** = *Chi square test*; **2** = *independent-samples t-test*.

3.2.2. Intra-group differences

3.2.2.1. Patients without relapse. No statistically significant differences in age or gender were found in the relapsing group between BD and SAD patients. Globally, no statistical differences were found between BD and SAD without relapse subgroups in emergency attendances, suicidal or violent acts.

3.2.2.2. Patients with relapse. No statistically significant differences in age or gender were found in the BD and SAD patients with relapse. SAD patients with relapse did not present higher hospitalizations compared to BD patients (1.2 ± 0.5 vs. 1.2 ± 0.4, ns). SAD patients predictably presented psychotic relapses, but BD patients in change presented with significantly more pure manic (0.3 ± 0.5 vs. 0.0 ± 0.2, Mann-Whitney 423.0, p = 0.028) and depressive episodes (0.3 ± 0.5 vs. 0.0 ± 0.0 Mann-Whitney = 390.0, p = 0.004). No significant differences in emergency attendances, suicidal acts and violent behaviors were recorded, but SAD patients committed more violent behaviors exclusively during acute pure psychotic episodes (n = 6, 23.1%), whilst BD patients during purely manic (n = 4, 9.8%) or mixed (n = 2, 4.9%) episodes.

3.3. Indirect measures of psychopathological compensation

Patients without relapse showed a significantly higher mean number of treatments at T0, "major" treatments (p = 0.01), combined with benzodiazepines (p = 0.012) or total (p = 0.028). Total changes, specific changes in antidepressants, antipsychotics and mood-stabilizers were significantly higher in the relapsing group (all p < 0.0005), as well as the total number of antipsychotics used during IY (p < 0.0005). Prevalent use and beginning of treatment with long-acting injectable drugs were significantly higher in relapsing patients (p = 0.005 and p < 0.0005 respectively), as well as treatment with electroconvulsive therapy (ECT, p = 0.012) (Table 3).

3.3.1. Intra-group differences

3.3.1.1. Patients with relapse. BD patients with relapse showed significantly more frequent changes in mood-stabilizer medication

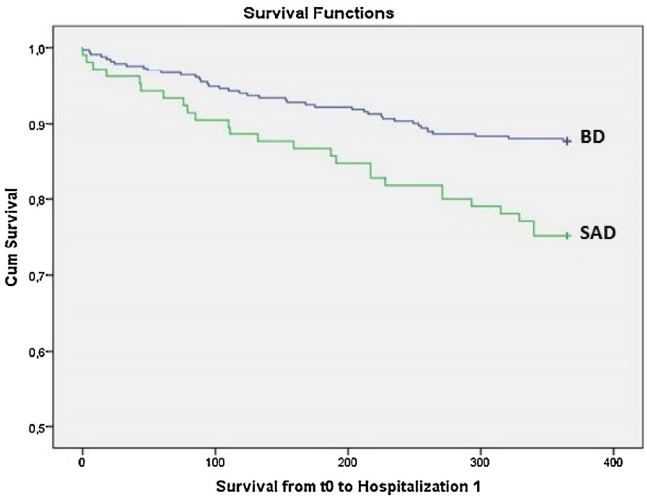

Fig. 2. Kaplan–Meier curves for time to hospitalization. **BD** = *Bipolar disorder, type I*; **SAD** = *Schizoaffective disorder, bipolar subtype*. Relapses: SAD (n = 26/105, 24.8%) vs. BD (n = 41/332, 13.3%), $\chi^2 = 9.468$, p = 0.002. Mean time ± SD to hospitalization: SAD = 312.16 ± 10.62 days vs. BD = 337.62 ± 4.43 days, Mantel Cox $\chi^2 = 9{,}421$, p = 0.002.
Note: Hospitalization was decided when an acute exacerbation of manic, psychotic, suicidal symptoms, was present or whereas psychomotor agitation, aggressiveness and/or lack of insight and need for treatment could impair patients' safety.

Table 2
Differences among patients relapsing and not relapsing.

	No relapse (n = 370)		**Relapse** (n = 67)			
Variables	**(n or mean)***	**(% or SD)**	**(n or mean)***	**(% or SD)**	**Test**	**P**
Female gender	202	54.6	38	56.7	0.103[1]	0.748
Age (years)	53.29	±37.10	47.97	±14.56	1.057[2]	0.305
Diagnoses						
BD	291	78.6	41	61.2	9.468[1]	**0.002**
SAD	79	21.4	26	38.8		
Emergency attendances						
-Yes	22	5.9	17	25.4	26.341[1]	<**0.0005**
-Number	0.80	±0.36	0.57	±1.50	24732.0[3]	<**0.0005**
Suicide attempts						
-Yes	0	0.0	5	7.5	27.932[1]	<**0.0005**
-Number	0.00	±0.00	0.07	±0.27	13320.0[3]	<**0.0005**
Violent behaviors						
-Yes	1	0.3	11	16.4	55.387[1]	<**0.0005**
-Number	0.00	±0.52	0.22	±0.55	14582.5[3]	<**0.0005**
-During Episode						
Mania	0	0.0	4	6.0	22.294[1]	<**0.0005**
Mixed	1	0.3	6	9.0	11.096[1]	**0.023**
Psychotic	0	0.0	2	3.0	27.147[1]	<**0.0005**

Notes: BD = *Bipolar Disorder type I*; **SAD** = *Schizoaffective disorder, bipolar type*.
Type of statistical test: 1 = *Chi square;* **2** = *independent-samples t-test*; **3** = *Mann-Whitney*.
* *Mann-Whitney test was used for non-parametric variables. Means and standard errors are reported in the table for descriptive purpose.*

compared to relapsing SAD patients (0.9 ± 1.2 vs. 0.2 ± 0.4, Mann-Whitney = 355.5, p = 0.008) and an overall significantly higher number of mood-stabilizers used during IY (1.4 ± 0.7 vs. 0.8 ± 0.7, Mann-Whitney = 2.81.5, p < 0.0005).

3.3.1.2. Patients without relapse. At T0, SAD patients without relapse showed significantly higher number of major treatments (2.8 ± 1.2 vs. 2.3 ± 1.0, Mann-Whitney = 13,665.6, p = 0.007), major treatments with benzodiazepines (3.2 ± 1.3 vs. 2.8 ± 1.2, Mann-Whitney = 13.473.0, p = 0.015) and total treatments (3.6 ± 1.6 vs. 2.9 ± 1.3, Mann-Whitney 14.009-5, p = 0.002). At the end of IY, SAD patients showed a significant total number of treatments (3.5 ± 1.4 vs. 3.1 ± 1.4, Mann-Whitney = 13.248.0, p = 0.033). No significant differences were found in total and specific changes in antidepressants, antipsychotics and mood-stabilizers, but SAD patients without relapse showed a significant higher number of antipsychotics tried during IY (1.7 ± 0.9 vs. 1.0 ± 0.8, Mann-Whitney 16609.5, p < 0.0005) and lower number of mood-stabilizers tried during IY (0.9 ± 0.7 vs. 1.2 vs. 0.6, Mann-Whitney = 8132.0, p < 0.0005). Also, SAD without relapse were more frequently on long-acting injectable treatment than BD patients without relapse (15, 19.0% vs. 12, 4.1%, $X^2 = 20.291$, p < 0.0005)

3.4. Prediction of hospitalization by diagnostic subgroups

We performed two Cox-Regression analyses on diagnostic subgroups in order to detect possible factors contributing to risk of hospitalization.

3.4.1. Bipolar subgroup

Cox-Regression analysis for BD subgroup was overall statistical significant ($\chi^2 = 494.819$, df = 10, p < 0.0005). Variables with a single significant contribution were: suicide attempts

Table 3
Differences in indirect (treatment) measures of psychopathological compensation in diagnostic subgroups.

	No Relapse (n = 370)		Relapse (n = 67)			
Variables	(mean)*	(SD)	(mean)*	(SD)	Test	
N of drugs at T0:					**M-W**	**P**
Major	2.41	±1.07	2.04	±1.17	10066.51	**0.010**
Major + BZD	2.85	±1.23	2.45	±1.41	10072.5	**0.012**
Total	3.08	±1.40	2.72	±1.71	10346.5	**0.028**
N of drugs at T1:						
Major	2.46	±1.05	2.42	±0.781	12.294.0	0.911
Major + BZD	2.92	±1.21	2.94	±0.95	12572.0	0.847
Total	3.18	±1.38	3.22	±1.20	12665.6	0.770
N of Changes						
Total changes	0.67	±1.37	3.82	±2.73	21642.0	<**0.0005**
- in antidepressants	0.23	±0.83	0.52	±0.88	14894.0	<**0.0005**
- in antipsychotics	0.34	±2.61	2.61	±2.16	21405.5	<**0.0005**
- in mood stabilizers	0.08	±0.31	0.60	±0.99	16242.5	<**0.0005**
Drugs tried in 365 days:						
N of antidepressants	0.47	±0.73	0.51	±0.70	12825.5	0.595
N of antipsychotics	1.14	±0.88	2.10	±0.92	19198.0	<**0.0005**
N of mood stabilizers	1.14	±0.66	1.16	±0.73	12737.5	0.682
	n	**(%)**	**n**	**(%)**	χ^2	**P**
Long-Acting Injectable						
Yes	27	7.3	12	17.9	7.861	**0.005**
In during the IY	6	1.6	10	14.9	28.465	<**0.0005**
Out during the IY	6	1.6	2	3.0	0.587	0.444
On ECT	13	3.5	7	10.4	6.246	**0.012**

Notes: BD = *Bipolar Disorder*; **BZD** = *Benzodiazepines*; **ECT** = *Electroconvulsive Treatment;* **IY** = *Index Year*; **N** = *Number*; **SAD** = *Schizoaffective Disorder;* **T0** = *Beginning of IY*; **T1** = *Conclusion of IY.*
Tests: M–W = *Mann-Whitney test;* χ^2= *Chi square test.*
* *Mann-Whitney test was used for non-parametric variables. Means and standard errors are reported in the table for descriptive purpose.*

(HR = 13.0, 95%CI = 4.0–42.0, p < 0.0005), purely manic first relapse in IY (HR = 12.5, 95%CI = 5.7–23.0, p < 0.0005), purely depressed first relapse in IY (HR = 9.8, 95%CI = 4.2–23.0, p < 0.0005), violent behavior during mixed phase (HR = 9.1, 95%CI = 1.8–45.4, p = 0.007), violent behavior during manic phase (HR = 6.8, 95% CI = 2.3–20.8, p = 0.001), total number of antipsychotics tried in IY (HR = 1.5, 95%CI = 1.1–2.2, p = 0.025), total number of emergency attendances (HR = 1.5, 95%CI = 1.2–1.8, p = 0.050), and changes in antipsychotics (HR = 1.3, 95%CI = 1.1–1.6, p = 0.003).

3.4.2. Schizoaffective subgroup

Cox-Regression analysis for SAD subgroup was overall statistical significant (χ^2 = 357.845, df = 9, p < 0.0005). Variables with a single significant contribution were: violent behavior during purely psychotic phase (HR = 12.1, 95%CI = 3.3–43.5, p > 0.0005), purely psychotic first relapse in IY (HR = 9.9, 95% CI = 4.0–24.7, p < 0.0005), suicide attempts (HR = 9.1, 95% CI = 2.7–30.7, p < 0.0005), changes in antipsychotics (HR = 1.6, 95%CI = 1.3–1.9, p < 0.0005), total number of emergency attendances (HR = 1.5, 95%CI = 1.2–1.9, p < 0.0005), and total drugs at T0 (HR = 1.3, 95%CI = 1.1–1.5).

4. Discussion

Our prospective naturalistic 1-year follow-up study comparing BD with SAD patients revealed some clinical relevant results. First of all, the hospitalization rate during the one-year follow-up was significantly higher in the SAD sample than in the BD subgroup (24.8% vs. 12.3%). Secondly, when relapsing, the diagnostic subgroups did not present differences in overall number of hospitalizations, yet SAD almost invariantly relapsed into psychotic episodes, while BD patients more frequently into pure mania and depression. Overall, SAD and BD subgroups seem to confirm a differential severity in the course of illness measured as time to hospitalization and acute clinical exacerbation, with SAD being the more severe condition. Yet, these diagnostic labels may be not informative on the actual prognosis of the patients. Thirdly and as expected, all patients with a relapse presented statistically more frequently signs of psychopathological unbalance such as suicide attempts, emergency attendances, and violent behaviors. Subpopulations at risk for worst outcomes should be defined in order to improve the prognostic value of a diagnosis. For instance, a careful evaluation of symptom dimensions would allow for better defining, addressing and managing critical treatment targets [28,29].

Furthermore, hetero-aggressiveness with violent behaviors played a major role in predicting hospitalization in our sample, as SAD patients presenting violent behaviors during a purely psychotic episode had a 12-fold increased risk to hospitalization, while BD present a 9-fold increased risk when presenting violent behaviors during mixed phase and 6-fold increased risk when presenting violent behaviors during manic phase. According to national surveys, the prevalence of violence in the general population is about 2% while it ranges from 0.8 to 34.7% in samples including individuals with mental illness, depending on the psychiatric disorder considered [30]. The relevance of aggressiveness as a cross-diagnostic negative prognostic factor finds ground on its frequent association with BD, especially in acute mixed phases [31], and it seems an even more important factor in SAD populations [32]. Common shared genetic liability could be hypothesized, as, for instance, neuronal splicing regulator RBFOX1 has been found associated to BD [33] as well as schizophrenia [34], and, more recently, to violent aggressive behavior [35]. On the other hand, it is possible that biological bases underpinning aggressive behavior only partially relate with a clinical syndrome, e.g. psychosis. A recent study outlined that lower levels of morning cortisol and cortisol variability significantly related to both aggression and psychosis, but independently, and no correlation with age, gender or psychosis severity or duration [36]. In this sense, categorical diagnoses predictably show a limited predictive validity, and the clinical assessment of patients could benefit from a different type of stratification considering, for instance, high levels of impulsivity, hostility,

positive symptoms and substance use, low level of insight and low social functioning [37].

In our study, self-aggressiveness also plays a major role in predicting hospitalization. SAD patients presented in our sample a 9-fold increased risk for hospitalization while BD patients presented a 13-fold increased risk when presenting suicidal acts. Conceptualization of suicide and aggressive/violent acts tends to a semantic similarity, framing these behaviors as self- and hetero- aggressiveness. A partial overlap in clinical presentation, with a possible predictive role of hetero-aggressiveness for suicidality, is possible [38] and could recognize a shared liability for impulsivity [39,40]. Yet, these behaviors could also derive from different symptoms dimensions, as well as genetic or biological mechanisms [41].

Interestingly, violent behaviors occurred only during acute episodes in our study. This has to be emphasized, and seems reinforced when considering the struggle for symptom control. In fact, relapsing patients presented more frequent changes in overall major treatments. Interestingly, patients not relapsing during IY presented a *higher* number of treatments at T0. In our regression models, both diagnostic subgroups presented more frequent changes in antipsychotic medications (and total antipsychotics tried in IY in bipolar subsample). Notably, average drug combinations in our study fall far beyond clinical guidelines recommendations [42,43]. The high rates of relapses in SAD populations might derive from the severity of the disease or from the lack of efficacy of current treatment options, undetected by pure populations recruited in randomized clinical trials. Also, it is possible that the frequent use of polypharmacy combinations stretching beyond evidence-based practices, produces complex interactions [44,45]. In the real-world, there is a clinical need for specifically tailored treatment plans, paradoxically and unanimously suggested by the very same guidelines.

On the other hand, past studies agree on the need for proper symptomatic and clinical management for better illness and overall health outcomes [46], but mortality rates in severe mental illness could derive from iatrogenic effects [47] as well as from an *under-prescription* for other comorbid medical conditions [48,49]. So, caution must be called for the risk of cumulative prescription and subsequent overtreatment [24].

When considering the role of aggressiveness in our study, evidence supports a benefit of second-generation antipsychotic medication in its management in psychotic conditions, with no apparent influence of mood-stabilizers or antidepressants [50,51], yet the benefit of beginning or suspending of the latter may clearly relate to acute mood prevention that in our sample invariably associated with such behavior [52].

Stabilized, SAD patients without relapse presented higher number of tried and actual treatments compared to BD patients without relapse. The use of long-acting injectable antipsychotics failed to ensure a good control of symptomatology in our study, which is in accordance with previous data that reported increased odds for relapse despite of an evidence of their efficacy [53]. This apparent contradiction could result from a selection bias for candidates to these treatments, tolerability issues, or anyway an improvement compared to previous course of illness for these patients. Unluckily, the design of our study did not allow for a throughout analysis of this aspect.

Lastly, we found in our study that frequent emergency attendances constitute a clear signal of increased risk for acute relapse. It is possible that psychosocial interventions aimed at an improving insight and awareness in patients and caregivers alike contribute to this effect [54,55]. Hereby, patients might benefit from further psychosocial/psychotherapeutic interventions aimed at encompassing cognitive deficits in a preventive way [56], impaired functioning [57], or untreated adverse events [58].

Some limitations of our work have to be taken into consideration. In order to minimize selection bias, the choice of the Index Year was performed *a priori*. Yet, a selection bias may not be excluded. Another limitation is the choice of considering a change of treatment as a measure of psychopathological compensation, as to say of efficacy, whilst it may also represent a measure of tolerability of the treatments prescribed. However, this possible bias was true for both BD and SAD diagnostic subgroups. Average doses of drugs used would have been ideal, yet the overall sample size did not allow for a dose-specific analysis. Recollection of other variables would have been also informative (e.g., number and type of previous episodes), but data were not collected in the clinical corresponding histories.

Compared to BD, SAD patients present a more severe course of illness measured as time to hospitalization. Violent acts towards selves (BD) or others (SAD) strongly predict a worse course of illness and may represent strategic therapeutic targets. Interventions aimed at improving patients' and caregivers' awareness on the disorder should be systematically implemented, as increased emergency attendances signal at-risk situations and would possibly allow for recurrence prevention. Increased emergency attendances should call for optimized combination treatments, warranting an improved control over symptoms, thus delaying hospitalizations.

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Declaration of Competing Interest

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- Norma Verdolini, Gerard Anmella, Isabella Pacchiarotti, Juan Undurraga, José M. Goikolea, Benedikt L. Amann, Andre F. Carvalho declare no conflict of interest.

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