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Original Article

Risk factors for rapid cycling in bipolar disorder

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Objectives: The aim of this study was to investigate the clinical factors associated with the development of rapid cycling, as well as to elucidate the role of antidepressants.

Methods: The present study (NCT01503489) is a prospective, naturalistic cohort study conducted in a sample of 289 patients diagnosed with bipolar disorder followed and treated for up to 14 years. The patients were divided into two groups on the basis of the development of a rapid cycling course (n = 48) or no development of such a course (n = 241), and compared regarding sociodemographic, clinical, and outcome variables.

Results: Among the 289 patients, 48 (16.6%) developed a rapid cycling course during the follow-up. Several differences were found between the two groups, but after performing Cox regression analysis, only atypical depressive symptoms (p = 0.001), age at onset (p = 0.015), and number of suicide attempts (p = 0.030) persisted as significantly associated with the development of a rapid cycling course.

Conclusions: The development of rapid cycling during the course of bipolar disorder is associated with a tendency to chronicity, with a poorer outcome, and with atypical depressive symptomatology. Our study also suggests that the development of rapid cycling is associated with a higher use of antidepressants.

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Dunner and Fieve (1) introduced in 1974 the concept of rapid cycling (RC), a course variant of bipolar illness that has been observed in the pre-pharmacologic era as well in modern studies, and incorporated into DSM-IV as a course specifier for bipolar disorder in patients with four or more episodes of illness within a year, in no particular pattern or sequence. The authors concluded that patients with four or more episodes per year were more likely to be non-responders to lithium (2). There is currently no evidence for a more valid cut-off to discriminate between RC and no RC (3, 4). Some patients experienced very brief cycles lasting for days (ultra-rapid cycling) or <1 day (ultradian cycling) (5, 6). The estimated prevalence of RC in bipolar disorder is around 12–24% at specialized mood disorder clinics; however, RC is a transient phenomenon in many patients (3, 7–13).

RC has been related to female gender (11, 14–16), bipolar disorder type II (8, 11, 13), child and adolescent bipolar disorder (17), early age of onset (16, 18–20), longer length and higher number of episodes experienced from the beginning of the

illness until the first psychiatric treatment (16, 19), higher comorbidity with other mental disorders such as alcohol and substance abuse and anxiety disorders (3, 15, 20, 21), episodes of depression of greater severity and poor response to any treatment (19), poorer global functioning (15, 16), poor outcome (15, 16, 20, 22), increased risk of suicide attempts (15, 19, 20, 23, 24), depressive predominant polarity (19, 20, 25), low thyroid function (26), family history of mood disorders (20, 27), more mixed states (28), and a relative resistance to all standard pharmacologic treatments and not just lithium (1, 2, 9, 12, 19–21, 29–31).

Focusing on the reported overrepresentation in female patients, the pathophysiology behind this finding remains unknown (12).

A meta-analysis of 10 studies including 2,057 patients with bipolar disorder (including 498 with RC) concluded that women were at somewhat more risk of developing RC than men (29.6% for women versus 16.5% for men). This analysis included all of the studies found that had data permitting computation of rates of rapid cycling in women and men with bipolar disorder, being this characteristic and the large sample the strengths of the study. We might suggest that its weaknesses were that the study was limited by variance in patient selection and diagnosis, with a possible underreporting of men with RC and a possible overrepresentation of women among patients treated for major mood disorders (14).

Another meta-analyses of eight studies included 2,054 patients with bipolar disorder who were consecutively admitted to an inpatient or outpatient facility, with RC present in 16.3% of the patients. Female gender had a small, but statistically significant, effect. The large sample of patients, without *a priori* selection for RC, was the main strength of the study. We might point out that a weakness of this study was that there was no matching in terms of numbers of patients with and without RC (11), but this was a meta-analysis of cohort studies and therefore the proportions of the two groups were representative of the numbers present in each cohort.

Other studies, though, have not confirmed the overrepresentation of female patients in those with RC, although female patients are more likely to have a predominantly depressive polarity of episodes over their lifetime (32).

There is controversy as to whether antidepressants (ADs) can trigger and prolong RC.

Regarding the association between use of ADs and the development of an RC course, Bunney et al. (33) postulated that switching from depression to hypomania involves a more active biological process than vice versa, reflecting an underlying vulnerability to RC.

Some longitudinal, observational studies have implicated both brief and prolonged AD drug use as being associated with an increased risk of RC (34, 35). Koukopoulos et al. (36) noted that AD use caused acceleration in the cycle frequency from 0.8 episodes per year prior to treatment to 6.5 episodes per year. Wehr et al. (37) reported that continued administration of AD drugs was responsible for RC in approximately 50% of 51 patients with bipolar disorder. Other investigators have estimated that 20% of all cases of RC are caused by AD treatment and that 95% of cases of spontaneous RC may worsen with the use of ADs, mainly tricyclics (5).

In fact, tricyclic ADs are the pharmacological group most frequently associated with the development of RC (38). In contrast, in a long-term follow-up study, Coryell et al. (19) found no association between tricyclic ADs and either RC or switching from depression to hypomania. Furthermore, there is some evidence that more selective ADs (selective serotonin reuptake inhibitors, bupropion, and others) may have a lower risk of inducing cycling acceleration (39–42). In a naturalistic study by Bauer et al. (43), using self-reported data, patients who were taking second- and third-generation ADs with a concurrent mood stabilizer did not experience an increase in the rate of RC.

It has been suggested that the association between ADs and RC may be related more to the frequent occurrence of depression or to a natural course of mania following depression than to the AD itself (7), but many authors (44) recommend the use of ADs only with an anti-manic agent.

In this study, we tried to elucidate the factors associated with the development of an RC course in patients with bipolar disorder, in a study with a prospective and longitudinal design, and the role of ADs. The identification of risk factors is extremely relevant from the clinical point of view.

We hypothesized that RC bipolar disorder is associated with more chronicity, poor outcome, and more AD prescriptions.

Materials and methods

Study design and participants

The present study was a prospective, naturalistic cohort study conducted in a sample of 289 patients diagnosed with bipolar I and bipolar II disorders according to DSM-IV criteria. The study design was approved by the Ethical and Research Committee of the Hospital Clínic of Barcelona. All

patients provided signed informed consent. The study is registered at clinicaltrials.gov (identifier: NCT01992302). Patients were recruited from Spanish primary care and other psychiatric centres, and were subsequently referred to the Bipolar Disorders Program of the Hospital Clínic and University of Barcelona (Catalonia, Spain) (45). Our Program is a specialized unit which provides treatment to all patients with bipolar disorder from a specific catchment area of Barcelona as well as difficult-to-treat patients from other parts of Spain (46). These patients were initially recruited during a non-euthymic state [i.e., current major depressive episode: Hamilton Depression Rating Scale-17 (HDRS-17) (47) score >20; or hypomanic episode: Young Mania Rating Scale (YMRS) (48) score >14; or manic episode: YMRS score >20; or mixed episode: YMRS and HDRS-17 scores >14] and followed and treated for up to 14 years. During the follow-up, all the episodes were registered. A patient was considered as an AD medication user if the AD was used for an appropriate period of time and at a dose that was considered within the potential efficacy range, according to the drug technical datasheet. A total of 416 patients were initially included in our sample, but 127 were excluded due to lack of relevant data (i.e., lack of prior information when referred to our tertiary center), death of the participant, or voluntary drop-out from the study; the proportion of drop-out patients was 30%. The remaining 289 patients with bipolar I and bipolar II disorder were divided into two groups on the basis of the development of an RC course (defined as having four or more depressive, hypomanic, manic, or mixed episodes during a period of one year) (n = 48) or no development of such a course (n = 241) during the follow-up period (mean duration for all patients = 9.05 ± 5.27 years, and specifically 9.63 ± 4.57 years for the RC group, and 8.93 ± 5.41 years for the non-RC group).

Information on several clinical variables was obtained from structured interviews with patients and their relatives (when available), including the number and polarity of lifetime episodes, the number of hospitalizations, age at onset, lifetime history of psychotic symptoms, psychiatric comorbid disorders, and suicidal behavior. Previous and current pharmacological and electroconvulsive treatment details were also recorded.

Several other variables were specifically assessed and included demographic data, seasonality according to the DSM-IV criteria, polarity of the first episode, psychiatric history of first-degree relatives, and treatment adherence. Information pertaining to social and occupational functioning was also recorded.

Procedures and outcomes

We used both Structured Clinical Interview for DSM-IV (SCID) Axis I (SCID-I) (49) and Axis II (SCID-II) (50) to confirm diagnoses. Sociodemographic, clinical, outcome, and pharmacological data were collected via a structured interview with patients and relatives (when available). Spanish validated versions of the HDRS-17 and the YMRS (51, 52) were administered by trained raters to assess depressive and manic symptoms, respectively, at intervals of at least every three months when patients were euthymic, and more often when patients were in depressive, (hypo)manic, and mixed episodes.

To define specific course and outcome indicators, we chose operational definitions of current mood episode, response, remission, recovery, relapse, recurrence, mood switch, and treatment-emergent mood switch similar to the definitions developed by the Task Force of the International Society for Bipolar Disorders (ISBD) (53) (Table 1). Suicidality was measured by the (i) number of attempts, (ii) violence and degree of lethality of the method employed, and (iii) severity of suicidal ideation (using the suicide item of the HDRS-17 and/or specific questions during the interview).

A depressive episode was considered as an atypical depression when, following DSM-IV-TR criteria, it was characterized by (i) mood reactivity and (ii) at least two of the following: significant weight gain or increase in appetite/hypersomnia/leaden paralysis/long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment; and (iii) criteria were not met for melancholic depression or catatonic depression during the same episode.

Statistical analysis

We used the Statistical Package for the Social Sciences [(SPSS) version 16 for Windows; SPSS, Inc., Chicago, IL, USA] for statistical analysis.

The two groups were compared for clinical, outcome, and sociodemographic characteristics, by ANOVA for continuous variables and by chi-square test for qualitative variables, as appropriate. Parametric tests were used according to sample distribution. All p-values were two-tailed and statistical significance was set at $p < 0.05$.

A proportional hazard model (Cox regression) was used to identify factors associated with the development of an RC course during the illness. The development of an RC course during the

Table 1. Course and outcome indicators similar to the definitions developed by the Task Force of the International Society for Bipolar Disorders (53)

	HDRS-17 score	YMRS score	HDRS-17/YMRS	Time interval	Description
Current major depressive episode	>20			At least 2 weeks	
Current hypomanic episode		>14		At least 4 days	
Current manic episode		>20		At least 7 days	
Current mixed episode			HDRS-17 and YMRS scores >14	At least 7 days	
Response to antidepressant	Reduction of at least 50% of HDRS-17 score of pretreatment symptom severity				
Bipolar depression: remission	≤7				
Bipolar mania: remission		≤7			
Recovery					8 consecutive weeks characterized by the absence of depressive and manic symptoms
Relapse					A new episode occurring within 8 weeks after having achieved remission from the previous episode
Recurrence					A new episode occurring >8 weeks after having achieved remission from the previous episode
Hypomanic/manic switch		YMRS score >14 within 8 weeks after the remission of the previous depressive episode			
Treatment emergent hypomanic/manic switch		YMRS score >14 within 8 weeks after the introduction or dose increase of an antidepressant			
Mixed switch			HDRS-17 and YMRS scores >14 within 8 weeks after the remission of the previous mood episode		
Treatment emergent mixed switch			HDRS-17 and YMRS scores >14 within 8 weeks after the introduction or dose increase of an antidepressant or antipsychotic		

Table 1. (Continued)

	HDRS-17 score	YMRS score	HDRS-17/YMRS	Time interval	Description
Depressive switch	HDRS-17 score >20 within 8 weeks after the remission of the previous manic episode				
Treatment emergent depressive switch	HDRS-17 score >20 within 8 weeks after the introduction or dose increase of an antipsychotic				

HDRS-17 = Hamilton Depression Rating Scale-17; YMRS = Young Mania Rating Scale.

follow-up was considered as the dependent variable and nine of the most significant variables (considered as independent factors) were: employment status, mixed episodes during the illness, atypical depressions, age at bipolar disorder onset, diagnostic delay (years), years of illness, number of ADs used during the follow-up, suicide attempts, and number of suicide attempts.

Results

Sample characteristics

Among the 289 patients with bipolar I and bipolar II disorder, 48 (16.60%) developed an RC course during the follow-up, while 241 (83.39%) did not. The two groups were comparable in terms of education, job qualification, work status, and autonomy.

Sociodemographic features

No gender differences were found between the two groups.

In terms of occupational functioning, we found significant differences in work status, with a more frequent active status in the non-RC group in comparison with the RC group (51% versus 27.1%, respectively; $p = 0.003$) (Table 2).

Clinical features

Regarding the type of bipolar disorder, no differences were found between the two groups.

There were differences regarding the mean duration of illness and the mean duration of diagnostic delay, with a longer course of disease for patients with RC (23.77 years versus 17.58 years in the non-RC group; $p < 0.001$), and a greater delay before correct diagnostic (9.15 versus 5.89 years, respectively; $p = 0.011$). We applied an ANCOVA in order to control for age in the relationship with the mean duration of illness, because a longer course of disease is highly correlated with age. We found that there were also significant differences between the two groups in the mean duration of illness when controlling for age.

No differences between the two groups were found regarding the age at bipolar disorder diagnosis, but the mean age at bipolar disorder onset was lower in the RC group in comparison with the non-RC group (24.54 versus 30.13 years, respectively; $p = 0.002$), the difference between the two groups remaining significant after applying Cox regression.

We did not find differences in the type of first affective episode, the presence of psychotic symptoms during the first episode, or the presence of psychotic symptoms in the follow-up period and

Table 2. Sociodemographic features differentiating rapid cycling patients and non-rapid cycling patients

	Total sample (N = 289) n (%)	RC group (n = 48) n (%)	Non-RC group (n = 241) n (%)	χ^2	p-value
Gender, male	139 (48.1)	20 (41.7)	119 (49.4)	0.953	NS
Work status, active	136 (47.1)	13 (27.1)	123 (51)	9.219	0.003

Non-RC = non-rapid cycling; NS = not significant; RC = rapid cycling.

not only during the first affective episode. But we found differences regarding the development of mixed episodes during the illness, which was significantly more frequent in the RC group in comparison with the non-RC group (45.8% versus 21.2%, respectively; $p = 0.001$).

No differences were detected regarding the existence of predominant polarity, familiarity, seasonality, and adherence to treatment. Similarly, there was no significant difference between the two groups in comorbidities, namely anxiety disorders, Axis II disorders, and alcohol and substance abuse disorders.

When comparing depressive characteristics between the two groups, we found a higher rate of atypical depressive symptoms among the RC patients in comparison with the non-RC group (75% versus 41.9%, respectively; $p < 0.001$). No differences were found regarding melancholic depressive symptoms or the presence of psychotic depression.

Interestingly, a greater mean number of ADs were prescribed in the RC group in comparison with the non-RC group (4.29 versus 2.70, respectively; $p = 0.002$) (Table 3). However, in order to control for the number of depressive episodes in the relationship with the number of ADs, we used an ANCOVA and found that the significant difference between the two groups was lost when the mean number of ADs was controlled for the number of depressive episodes.

Within the RC group, patients who had received tricyclic ADs together with selective serotonin reuptake inhibitors, and serotonin noradrenaline reuptake inhibitors (lifetime) constituted the largest group (27.1%), and only 8.3% had not received any AD. This last group (non-AD) was, in contrast, the largest within the non-RC sample (21.6%) (Fig. 1).

Outcomes

Focusing on the course of the illness, we found more patients with relapses during AD treatment and more patients with switches with ADs in the RC group than in the non-RC group (81.8% versus 56.1%; $p = 0.002$; 90.9% versus 63.5%; $p < 0.001$, respectively), but no differences were found between the two groups regarding responses to ADs. Regarding the quantitative characteristics, the RC group had a greater mean number of relapses during treatment with ADs than the non-RC group (5.93 versus 1.63, respectively; $p < 0.001$), a higher mean number of responses to

Table 3. Clinical features differentiating rapid cycling patients and non-rapid cycling patients

	Total sample (n = 289) n (%)	RC group (n = 48) n (%)	Non-RC group (n = 241) n (%)	χ^2	p-value
Type of BD, type I	204 (70.6)	36 (75)	168 (69.7)	0.540	NS
First episode, depression	176 (60.9)	33 (68.8)	143 (59.3)	1.490	NS
Psychotic symptoms at first episode	87 (30.1)	9 (18.8)	78 (32.4)	3.526	NS
Psychotic symptoms during illness	173 (59.9)	29 (60.4)	144 (59.8)	0.007	NS
Mixed episodes during illness	73 (25.3)	22 (45.8)	51 (21.2)	12.905	0.001
Predominant polarity	143 (49.5)	20 (41.7)	123 (51)	1.406	NS
Type of predominant polarity, depressive	79 (55.2)	15 (75)	64 (52)	3.670	NS
Family history of BD	122 (42.2)	21 (43.8)	101 (41.9)	0.056	NS
Seasonal pattern	71 (24.6)	13 (27.1)	58 (24.1)	0.197	NS
Treatment adherence, good	210 (72.7)	33 (68.8)	177 (73.4)	0.444	NS
Axis II comorbidity	64 (22.1)	12 (25)	52 (21.6)	0.272	NS
Anxiety comorbidity	111 (38.4)	24 (50)	87 (36.1)	3.269	NS
Alcohol abuse	70 (24.2)	12 (25)	58 (24.1)	0.019	NS
Substance abuse	87 (30.1)	13 (27.1)	74 (30.7)	0.250	NS
Atypical depression[a]	137 (47.4)	36 (75)	101 (41.9)	17.580	<0.001
Melancholic depression	105 (36.3)	21 (43.8)	84 (34.9)	1.369	NS
Psychotic depression	46 (15.9)	9 (18.8)	37 (15.4)	0.345	NS
	Mean (SD)	Mean (SD)	Mean (SD)	*t*-test	p-value
Age at BD onset[a]	29.20 (11.69)	24.54 (7.17)	30.13 (12.20)	9.412	0.002
Age at BD diagnosis	35.51 (13.22)	33.63 (11.90)	35.88 (13.46)	1.165	NS
Years of illness	18.61 (10.64)	23.77 (11.33)	17.58 (10.21)	21.160	<0.001
Diagnostic delay, years	6.43 (8.15)	9.15 (10.44)	5.89 (7.53)	6.506	0.011
No. of Ads	2.96 (2.58)	4.29 (3.27)	2.70 (2.34)	10.13	0.002

AD = antidepressant; BD = bipolar disorder; Non-RC = non-rapid cycling; NS = not significant; RC = rapid cycling; SD = standard deviation.

[a]Variables with significant differences between the two groups after performing a Cox regression analysis.

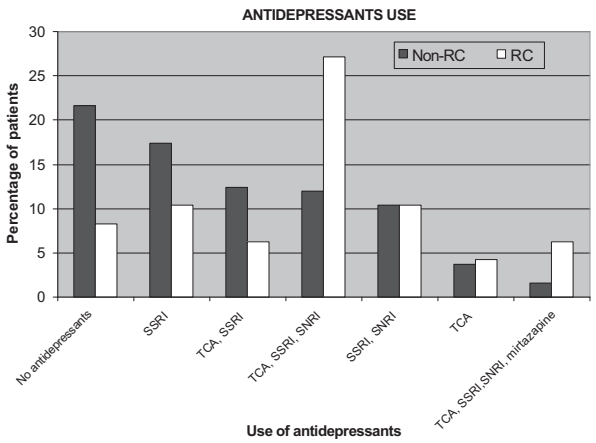

Fig. 1. Distribution of antidepressant prescription pattern in patients with and without rapid cycling (RC). TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin noradrenaline reuptake inhibitor.

ADs (5.57 versus 2.65, respectively; $p < 0.001$), and a greater mean number of switches from depression to hypomania, mania or mixed state with AD treatment (4.59 versus 1.22, respectively; $p < 0.001$).

The RC group presented with a greater mean number of total episodes in comparison with the non-RC group (31.17 versus 9.89, respectively; $p < 0.001$), as well as a higher mean number of depressive episodes (17.21 versus 5.16, respectively; $p < 0.001$), manic episodes (3.71 versus 1.91, respectively; $p < 0.001$), hypomanic episodes (9.00 versus 2.42, respectively; $p < 0.001$), and mixed episodes (1.25 versus 0.39, respectively; $p < 0.001$).

Likewise, the RC group had a greater mean number of hospitalizations (3.00 versus 1.90 in the non-RC group; $p = 0.003$).

Focusing on suicidality, we found significantly greater suicidal ideation and more suicide attempts in the RC group in comparison with the non-RC group (64.6% versus 36.9%; $p = 0.001$; 43.8% versus 14.9%; $p < 0.001$, respectively); similarly, the RC group showed a higher mean number of suicide attempts (0.90 versus 0.27 in the non-RC group; $p < 0.001$).

We also found that the use of electroconvulsive therapy was significantly more frequent in the RC group than in the non-RC group (33.3% versus 10.4%, respectively; $p < 0.001$) (Table 4).

The sociodemographic, clinical, and outcome characteristics that displayed significant differences ($p \leq 0.011$) between the RC and non-RC groups were treated as independent variables.

After running a Cox regression analysis, only atypical depressive symptoms, age at onset and number of suicide attempts were significantly associated with the development of RC during the illness (Table 5).

Discussion

RC is one of the main challenges in the management of bipolar disorder, a severe and chronic

Table 4. Outcome features differentiating rapid cycling patients and non-rapid cycling patients

	Total sample (n = 289) n (%)	RC group (n = 48) n (%)	Non-RC group (n = 241) n (%)	χ^2	p-value
Relapses during AD	142 (60.9)	36 (81.8)	106 (56.1)	9.930	0.002
Switches with AD	160 (68.7)	40 (90.9)	120 (63.5)	12.470	<0.001
Responses to AD	214 (91.8)	43 (97.7)	171 (90.5)	2.506	NS
Suicidal ideation	120 (41.5)	31 (64.6)	89 (36.9)	12.607	0.001
Suicide attempts	57 (19.7)	21 (43.8)	36 (14.9)	20.987	<0.001
ECT	41 (14.2)	16 (33.3)	25 (10.4)	17.332	<0.001
	Mean (SD)	Mean (SD)	Mean (SD)	*t*-test	p-value
Relapses during AD, n	2.44 (3.66)	5.93 (5.87)	1.63 (2.27)	62.01	<0.001
Switches with AD, n	1.85 (2.55)	4.59 (3.97)	1.22 (1.50)	84.95	<0.001
Responses to AD, n	3.20 (3.61)	5.57 (6.39)	2.65 (2.27)	25.72	<0.001
Episodes, n					
Total	13.42 (13.52)	31.17 (21.51)	9.89 (7.29)	16.155	<0.001
Depressive	7.16 (8.41)	17.21 (14.33)	5.16 (4.52)	21.581	<0.001
Manic	2.21 (2.85)	3.71 (4.58)	1.91 (2.26)	6.715	<0.001
Hypomanic	3.52 (4.97)	9.00 (7.96)	2.42 (3.16)	10.545	<0.001
Mixed	0.53 (1.25)	1.25 (1.89)	0.39 (1.03)	10.208	<0.001
Hospitalizations, n	2.08 (2.33)	3.00 (2.92)	1.90 (2.16)	7.551	0.003
Suicide attempts, n[a]	0.37 (0.91)	0.90 (1.32)	0.27 (0.76)	26.029	<0.001

AD = antidepressant; ECT = electroconvulsive therapy; Non-RC = non-rapid cycling; NS = not significant; RC = rapid cycling; SD = standard deviation.
[a]Variables with significant differences between the two groups after performing a Cox regression analysis.

Table 5. Results from Cox regression analysis

	β	Wald	p-value	Hazard
Atypical depression	1.178	11.079	0.001	3.247
Age at onset	−0.044	5.890	0.015	0.956
No. of suicide attempts	0.252	4.695	0.030	1.287

Results showed that only *atypical depressions*, *age at onset* and *number of suicide attempts* were significantly associated with the development of a rapid cycling course.

illness. This study was carried out in order to investigate the clinical factors associated with the development of RC during the course of the illness in patients with bipolar disorder, as well as to elucidate the role of ADs in the course and outcome of the disease.

According to our findings, the occurrence of RC is associated with a tendency to chronicity, a poorer outcome, a greater use of ADs, and atypical depressive symptoms.

Surprisingly, in the present study, 16.6% of patients with bipolar disorder developed RC during the course of illness. Although this is in accordance with existing literature (3, 7–12), we expected a higher percentage of RC because of the high proportion of difficult-to-treat patients in our sample.

No gender differences were found between the two groups, in contrast with some previously published reports (11, 14). A plausible explanation for the relationship between RC and female gender is that women have a greater predominance of depression, which probably leads to an increased use of ADs (7, 42, 54). Thyroid alterations, which are more frequent among women, have also been associated with a higher probability of developing RC. Nonetheless, in our sample, we did not find statistically significant differences between women and men in terms of the number of depressive episodes ($t = 1.044$, $p = 0.297$), the number of ADs ($t = 1.540$, $p = 0.125$), predominant polarity ($\chi^2 = 0.792$, $p = 0.374$), and the type of predominant polarity ($\chi^2 = 2.749$, $p = 0.097$). This is our explanation as to why no gender effect was seen on RC in our sample. Perhaps in other settings, where the use of ADs might be more liberal, the reported association between RC and female gender might be confirmed, but at least in our sample there was no signal of gender effects on RC.

Similarly, we did not find that RC in patients with bipolar disorder was significantly associated with other psychiatric comorbidities (anxiety disorders, alcohol and substance abuse/dependence, and Axis II disorders).

According to our results, two factors indicate that the development of RC during the course of illness is associated with a tendency to chronicity: (i) a higher average number of years spent ill, and, especially after Cox regression, (ii) a younger age at onset in the RC group. We also found a longer diagnostic delay in the RC group, highlighting the importance of an early correct diagnosis, which implies correct treatment, which may lead to a better outcome. It is probable that an early correct diagnosis would have avoided the development of RC in a proportion of patients in the sample.

In our study, several indicators of longitudinal severity of disease were associated with RC, such as a greater suicidal ideation rate, a greater number of hospitalizations, a higher rate of non-active work status, more use of electroconvulsive therapy, and, especially after Cox regression, a higher number of suicide attempts. Hence, this study sheds further light on the reported association between suicidality and RC (23).

One of the most controversial topics in psychiatry nowadays is whether ADs may actually induce or worsen RC. We found that the RC group had been treated with a greater number of ADs during the course of illness. This finding, however, does not necessarily imply causality. In fact, when we controlled the relationship with the number of ADs for the number of depressive episodes in ANCOVA, the significant difference between the two groups disappeared. The RC patients had a higher number of total episodes in comparison with the non-RC group and also a higher number of depressive episodes, which are frequently treated with ADs, and this may be the main reason for their greater use. But we could also consider that greater use of ADs might precipitate the development of RC, especially when used in monotherapy. Further studies are needed to clarify the direction of the causality.

The literature examining the pharmacological treatment of RC is still sparse and there is therefore no clear consensus with respect to its optimal pharmacological management (55), but we suggest that the use of ADs in RC patients with bipolar disorder, as advised in the recent ISBD Consensus Report (56), is not to be recommended, and other pharmacological options such as atypical antipsychotics should be considered as a first-line therapy.

We found a large difference between the two groups regarding atypical depressive symptoms, with higher rates in the RC group. The presence of these symptoms can be recognized as an indicator of worse outcome for patients with bipolar disorder.

Limitations of this study include its unicentric nature, which may limit the generalizability of the

findings, the last-resort nature of the Barcelona Bipolar Program at Hospital Clínic, which might result in an overrepresentation of difficult-to-treat patients with a poorer course and illness outcome (57), a relatively small sample size, and the non-inclusion of thyroid status in the research protocol. Another limitation may be the naturalistic design of the study (poor internal validity—the researchers cannot control for most variables, some of which might be considered as potentially confounding), which may have allowed several potentially confounding variables to affect the results, but it is justified by the fact that the study was precisely designed to ascertain the variables associated with the development of RC in routine clinical practice.

Aside from the above-mentioned limitations, the strengths of this study include the long-term, prospective design combined with thorough retrospective assessment of some specific variables, and the systematization of variables resulting in sufficient statistical power to detect differences between the two groups. The fact that not all patients were treated with ADs during the illness adds additional strength to the study because this can help to clarify the role of the ADs in the course of the illness, especially in the development of RC. To the best of our knowledge, there are very few studies assessing the clinical factors associated with the development of RC and the impact of ADs on course and outcome in patients with bipolar disorder, and the results may provide important suggestions for daily clinical practice.

In conclusion, our study suggests that the development of RC during the course of bipolar disorder is associated with the use of ADs, not implying causality. This is, in our opinion, one of the most relevant findings of the study, providing important suggestions for daily clinical practice by warning against the over-prescribing of ADs, which could influence negatively the course of illness by precipitating RC, which is associated with a greater rate of suicide attempts. RC is also associated with an early age at bipolar disorder onset, highlighting the need for correct treatment at early stages. The association between atypical depressive symptoms and RC justifies its assessment, considering the possible association with a worse outcome of the illness.

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