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ORIGINAL ARTICLE

Psychiatric and clinical correlates of rapid cycling bipolar disorder: a cross-sectional study

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Objective: Rapid cycling (RC) is a feature of bipolar disorder (BD) that has been associated with worse outcome and more severe disability. Our goal was to investigate the association of demographic and clinical factors with RC.
Methods: We compared RC and non-rapid cycling (NRC) BD patients from the Brazilian Research Network in Bipolar Disorder (BRN-BD) regarding age at onset of BD; total number of episodes; previous number of manic, depressive, mixed, and hypomanic episodes; polarity of the first episode; gender; number of suicide attempts; number of lifetime hospitalizations and lifetime history of at least one hospitalization; family history of mood disorder; clinical comorbidities such as hypothyroidism, hyperthyroidism, seizures; and current use of medications such as lithium, anticonvulsants, antipsychotics, and antidepressants.
Results: We studied 577 patients and found that 100 (17.3%) met the criteria for RC in the year before the investigation. RC patients had earlier age at onset, longer duration of disease, more lifetime depressive and manic episodes, higher number of suicide attempts, and higher rate antidepressant use.
Conclusion: The presence of RC in the previous year was associated with specific clinical characteristics closely related to worse outcome in the course of BD.

Keywords: Bipolar disorder; age of onset; suicide; antidepressants

Introduction

Bipolar disorder (BD) is a chronic disease characterized by cyclic episodes of severe mood swings followed by periods of remission. The severity of episodes varies, and polarity might present as mania or depression. A bipolar cycle is defined as the interval between the onset of an episode of any polarity and the emergence of a new mood episode of any polarity.[1]

A cycling pattern is a key feature of the bipolar disorder. The duration and frequency of cycles vary from days to years. The term rapid cycling (RC) was first used in 1974 in reference to a group of lithium-unresponsive manic-depressive patients presenting at least four mood episodes in the previous year.[2] Currently, RC is a course specifier for BD in DSM-5,[3] and the original concept definition has been maintained. For episodes of the same polarity, a remission period of at least two months must occur to characterize RC bipolar disorder (RCBD). For episodes of opposite polarity, a remission period is not required.[3] The estimated 12-month prevalence of RCBD ranges from 9 to 32%, whereas the lifetime prevalence of RCBD ranges from 26 to 43%.[4-8]

Many studies have investigated the differences between BD patients with and without RC. In general, RCBD has been associated with worse disease outcome[9,10] and more severe disability.[7,11,12] More specifically, many factors have been described to be associated with RC, such as female gender,[5,13] earlier age at onset,[6,12] increased risk for suicide,[13,14] predominance of depression,[15,16] hypothyroidism,[6,17] bipolar type II disorder,[8,18,19] and higher rates of antidepressants use.[7,20] However, some of these associations are still controversial, and many studies have been criticized regarding aspects such as lack of a uniform definition of RC and use of heterogeneous samples. Thus, more studies are needed to clarify which factors are associated with the presence of RC in BD.

Our goal was to investigate the association of demographic and clinical factors with RC in a multicenter sample of BD patients (types I and II) from the Brazilian Research Network in Bipolar Disorder (BRN-BD).

Methods

We carried out a cross-sectional study of BD I and II outpatients enrolled in the BRN-BD from three specialized mood disorder centers in Brazil (cities of São Paulo, Porto

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Alegre, and Salvador using the same research protocol). Inclusion criteria were age $\geqslant$ 18 years and a diagnosis of DSM-IV BD type I or II. Exclusion criteria were schizophrenia or other psychotic disorders, schizoaffective disorders, and organic mental disorders. Diagnostic assessments were conducted by research-trained, board-certified psychiatrists. All patients were diagnosed using the Structured Clinical Interview for DSM-IV Disorders (SCID-I).[21] The following instruments were administered: Associação Brasileira de Transtorno Bipolar (ABTB, Brazilian Association for Bipolar Disorder) questionnaire for sociodemographic and clinical data; 17-item Hamilton Depression Rating Scale (HAMD-17) to assess severity of depressive symptoms[22]; and Young Mania Rating Scale (YMRS)[23] to assess severity of manic symptoms. Patients were classified as euthymic if they did not meet the criteria for any mood episode in the last 2 months based on the ABTB questionnaire and had HAMD-17 and YMRS scores lower than 7 in the week before the assessment.

RC was defined as four or more mood episodes in the previous year.[2] Patients were classified as having or not RCBD and prevalence of RCBD was determined in the study sample. After that, the group identified with RC was compared to the group of non-rapid cycling BD (NRC) patients regarding the following characteristics: age at onset of BD; lifetime number of episodes; lifetime number of manic, depressive, mixed, and hypomanic episodes; polarity of the first episode; gender; number of suicide attempts; number of lifetime hospitalizations and lifetime history of at least one hospitalization; family history of mood disorder; clinical comorbidities such as hypothyroidism, hyperthyroidism, seizures; and current use of medications such as lithium, anticonvulsants, antipsychotics, and antidepressants. The presence of lifetime migraine was also investigated and the results were published elsewhere.[24] The study protocol was approved by the Ethics Committee of each institution. All patients gave written informed consent and the procedures of the study were carried out according to the Declaration of Helsinki.

Statistical analysis

Statistical analysis was done using SPSS version 17.0. Categorical variables were analyzed using the Pearson chi-square test and the Fisher exact test. For continuous variables, differences between groups were tested using the Mann-Whitney test. Significance was set at α= 0.05.

Results

Sociodemographic and clinical characteristics

Our sample included 577 patients, of which 69.5% were female. BD type I was identified in 518 (89.8%) patients, BD type II in 45 (7.8%) patients, and BD not otherwise specified in 14 (2.4%) patients. Of the total sample, 100 patients (17.3%) had RC in the previous year. There were no statistical differences between the RC and NRC groups regarding mean age (RC = 39$\pm$10 years; NRC = 41$\pm$12 years; p = 0.098) and gender (female, RC = 76%; NRC = 69.4%; p = 0.188) (Table 1).

Age at onset was more than 4 years earlier in RC patients vs. NRC patients (RC = 21.2$\pm$12.2 years; NRC = 25.6$\pm$11.4 years; p = 0.000). RC patients also had longer duration of disease (RC = 19$\pm$14 years; NRC = 15$\pm$11 years; p = 0.011) and more lifetime mood episodes than NRC patients (RC = 28.4$\pm$22.3 episodes; NRC = 11.5$\pm$10.5 episodes; p = 0.000). This difference was significant for both manic (RC = 10.1$\pm$7.5 episodes; NRC = 6.0$\pm$6.3 episodes; p = 0.000) and depressive (RC = 14.3$\pm$20.2 episodes; NRC = 5.5$\pm$6.7 episodes; p = 0.000) episodes. However, there were no statistically significant differences between RC and NRC regarding the number of hypomanic and mixed episodes Family history of mood disorders was also similar in the two groups (RC = 55.1%; NRC = 47.3%; p = 0.160) (Table 1).

With respect to the first episode of the illness, there were no differences between the groups in terms of polarity (p = 0.053). For more than half the patients in both groups BD began with a depressive episode

Table 1 Demographic and clinical characteristics of BD patients

Characteristics	Cycling type		p-value*
	Rapid (n=100)	Non-rapid (n=477)	
Age (years)	39$\pm$10	41$\pm$12	0.098
Female sex	76 (76)	331 (69.4)	0.188
Age at onset (years)	21.2$\pm$12.2	25.6$\pm$11.4	0.000†
Family history of mood disorders	54 (55.1)	207 (47.3)	0.160
Suicide attempts (yes)	61 (63.5)	163 (38.6)	0.000†
Number of suicide attempts	2.3$\pm$4.3	1.3$\pm$5.4	0.000†
Hospitalization (yes)	58 (60.4)	306 (71.8)	0.028†
Number of hospitalizations	3.6$\pm$6.6	3.4$\pm$7.9	0.099
Disease duration (years)	19$\pm$14	15$\pm$11	0.011
Number of episodes	28.4$\pm$22.3	11.5$\pm$10.5	0.000†
Manic	10.1$\pm$7.5	6.0$\pm$6.3	0.000†
Depressive	14.3$\pm$20.2	5.5$\pm$6.7	0.000†
Hypomanic	0.9$\pm$3.7	0.2$\pm$1.1	0.240
Mixed	0.8$\pm$1.9	0.2$\pm$0.6	0.557

Data presented as mean $\pm$ standard deviation or n (%).
* Chi-square test/Fisher exact test or Mann-Whitney test.
† $p < 0.05$.

(RC = 57.1%; NRC = 57.6%). The second most common first episode was mania (RC = 25%; NRC = 34.1%), followed by mixed episodes (RC = 11.9%; NRC = 4.4%) and hypomania (RC = 2.4%; NRC = 1.3%). A higher number of patients from the RC group had attempted suicide at least once when compared to the NRC group (RC = 63.5%; NRC = 38.6%; p = 0.000). The RC group also had a higher mean number of lifetime suicide attempts (RC = 2.3±4.3; NRC = 1.3±5.4; p = 0.000). After dividing the mean number of suicide attempts by the number of years of disease, the suicidality rate remained higher in the RC group (RC = 0.19±0.39; NRC = 0.09±0.27; p = 0.000). The number of lifetime hospitalizations was similar in both groups (RC = 3.6±6.6; NRC = 3.4±7.9; p = 0.099), but a significantly higher percentage of NRC patients had been hospitalized when compared with RC patients (RC = 60.4%; NRC = 71.8%; p = 0.028) (Table 1).

Clinical comorbidities and current psychiatric treatments

We did not observe significant differences for hypothyroidism (RC = 21.1%; NRC = 16.9%; p = 0.345), hyperthyroidism (RC = 2.1%; NRC = 1.7%; p = 0.782), seizures (RC = 13.3%; NRC = 9.1%; p = 0.210), asthma (RC = 21.4%; NRC = 14.6%; p = 0.162), and diabetes mellitus (RC = 11.4%; NRC = 8.6%; p = 0.674) (Table 2).

Regarding current use of medication, the RC group had a higher rate of patients taking antidepressants (RC = 31.9%; NRC = 18.7%; p = 0.017) and a smaller rate using first-generation antipsychotics (RC = 24.6%; NRC = 38.1%; p = 0.037). There were no significant differences between the groups for use of lithium (RC = 66.7%; NRC = 68.3%; p = 0.797), anticonvulsants (RC = 63.8%; NRC = 51.9%; p = 0.77), and atypical antipsychotics (RC = 24.6%; NRC = 18.3%; p = 0.236) (Table 2). The association between antidepressants and RC was also present when only the subgroup of BD type I patients was considered (RC = 32.3%; NRC = 16.6%; p = 0.006).

Discussion

In the present sample, RCBD patients had earlier age at onset, longer duration of disease, more lifetime depressive and manic episodes, more lifetime suicidality, and a higher rate of antidepressant use when compared with NRC patients.

The finding of earlier age at onset of disease in RC patients has been consistently reported in the literature,[6,12,16,25,26] but the reason remains unclear. Some authors have argued that earlier age at onset may be linked to a kindling mechanism that will eventually lead to autonomous mood episodes that do not require a trigger.[25,27] Interestingly, this finding does not change when the polarity of first episode is taken into account.[6] However, controversy still exists, with one study having reported later age at onset for RC[28] and other studies reporting no difference in age at onset between RC and NRC.[7,29,30]

Another finding of the present study that is consistent with the literature is the higher number of suicide attempts and the higher proportion of suicide attempters in the RC group.[4,6,13,14] This might be explained by the usually longer duration of disease associated with RC, which would be related to the earlier age at onset discussed above. The longer duration of disease in RC patients would be associated with increased burden and neuroprogression, which would aggravate the overall outcome, including a higher risk of suicide.[31-33] However, further analysis of our results show that the mean number of suicide attempts per year of disease was still higher in the RC group, which could be attributed to its more complicated clinical picture. It is also important to note that other studies have also failed to establish an association between RC and suicidality.[12,34]

There is a controversy as to whether hypothyroidism contributes to the development of RC in patients with BD.[17] Several studies have found an association,[6,17,35,36] while others have not observed this finding.[37-39] Our study corroborates the notion that hypothyroidism and hyperthyroidism are not associated with RC.

Table 2 Medical comorbidities and current psychiatric treatment of BD patients

Characteristics	Cycling type		p-value*
	Rapid	Non-rapid	
Medical comorbidities			
Hypothyroidism	20 (21.1)	70 (16.9)	0.345
Hyperthyroidism	2 (2.1)	7 (1.7)	0.782
Seizures	13 (13.3)	40 (9.1)	0.210
Asthma	15 (21.4)	39 (14.6)	0.162
Diabetes mellitus	8 (11.4)	23 (8.6)	0.674
Current medication			
Antidepressants	22 (31.9)	50 (18.7)	0.017†
Typical antipsychotics	17 (24.6)	102 (38.1)	0.037†
Atypical antipsychotics	17 (24.6)	49 (18.3)	0.236
Lithium	46 (66.7)	183 (68.3)	0.797
Anticonvulsants	44 (63.8)	139 (51.9)	0.777

Data presented as n (%).
* Chi-square test/Fisher exact test.
† $p < 0.05$.

Confirming the findings of numerous previous studies,[6,7,13,17,20,38] we observed a higher rate of antidepressant use in the RC group. Some authors have found that the likelihood of cycling increases linearly with antidepressant use, with patients taking antidepressants being over three times more likely to have RC than patients who do not use antidepressants.[26] However, a causative association can be inferred only from prospective studies and, while some support this negative effect of antidepressants,[7,20,40] others did not find the same result.[4,5,41] Some researchers have argued that a non-causal relationship might explain this association, which they attribute to the predominant depressive polarity usually found in RC.[4]

Our study has some limitations. Its cross sectional design precludes the verification of causative associations. Also, a substantial percentage of our sample (62%) was not in an euthymic state. This might have influenced our results, since patients with mood symptoms might have changes in cognition that may bias the collection of data regarding longstanding events. However, in our study, this bias was minimized by checking the information with family members or in clinical records. Another limitation was the setting. Because the study was conducted in specialized and tertiary academic centers, generalization of the present results to other population is not recommended, since our patients tend to have more comorbidities, to be more refractory to treatment, and to present a worse course and outcome. Finally, we were unable to determine the temporal association of presence of RC with medication used and time of suicide attempts. Still, this study has strengths that deserve mention, such as a considerably large sample size and data collection by a specialized physician using structured interviews, ensuring high quality to our clinical data.

In summary, our study corroborates the idea that RCBD includes a distinctive and more symptomatic set of BD patients, and provides support to the existence of an association between RC and more suicide attempts, more antidepressant use, and earlier age at onset of BD.

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Disclosure

The authors report no conflicts of interest.

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