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Clinical Correlates of Patients With Rapid-Cycling Bipolar Disorder and a Recent History of Substance Use Disorder: A Subtype Comparison From Baseline Data of 2 Randomized, Placebo-Controlled Trials

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Abstract

Objective—To compare clinical variables in patients with rapid-cycling bipolar I or II disorder and a recent history of substance use disorder (SUD).

Method—Cross-sectional data from 2 studies of patients with rapid-cycling bipolar I disorder or rapid-cycling bipolar II disorder and a recent history of SUD were used to retrospectively assess the differences in clinical variables between the subtypes. The studies were conducted from November 1997 to February 2007 at University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio. Extensive clinical interview and the Mini-International Neuropsychiatric Interview were used to ascertain DSM-IV diagnoses of rapid-cycling bipolar disorder, SUDs, and other Axis I disorders and to collect clinical variables. The Addiction Severity Index (ASI), Global Assessment Scale (GAS), and the Medical Outcomes

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Drug names: divalproex (Depakote), lamotrigine (Lamicial and others), lithium (Lithobid, Eskalith, and others).

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Study 36-ltem Short-Form Health Survey were used to measure the severity of impairment at the initial assessment. One-way analysis of variance or χ^2 was used for significance tests. A Bonferroni adjustment was applied for multiple comparisons.

Results—Of 245 patients with rapid-cycling bipolar disorder (rapid-cycling bipolar I disorder, N = 191; rapid-cycling bipolar II disorder, N = 54) and a recent history of SUD, the demographics were similar. A significantly higher rate of panic disorder was observed in patients with rapid-cycling bipolar I disorder than in those with rapid-cycling bipolar II disorder (odds ratio = 3.72, 95% CI = 1.66 to 8.32, p = .008). A significantly higher psychiatric composite score on the ASI was also found in patients with rapid-cycling bipolar I disorder than in those with rapid-cycling bipolar II disorder even after Bonferroni adjustment (p = .0007). There were no significant differences between the subtypes in the rates of previous hospitalization or suicide attempt, early childhood verbal, physical, or sexual abuse, lifetime substance abuse or dependence, the number of SUDs or mood episodes in the last 12 months, and total or other subscale scores on ASI and GAS.

Conclusion—Except for the significantly higher rate of comorbid panic disorder and higher psychiatric composite scores on the ASI in patients with rapid-cycling bipolar I disorder than in those with rapid-cycling bipolar II disorder, the other clinical variables were similar between the 2 groups.

The differences between bipolar disorder types I and II were defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),[1] based mainly on the severity of symptoms, functional impairments, and duration of manic/hypomanic episodes. However, other differences between the 2 types have also begun to emerge. In prospective longitudinal studies, patients with bipolar II disorder experience 39 times more follow-up weeks with depressive symptoms than with hypomanic symptoms, whereas bipolar I disorder patients only experience 3 to 4 times more follow-up weeks with depressive symptoms than with manic symptoms.[2,3] Patients with bipolar I disorder and those with bipolar II disorder also respond to treatments differently. It has been reported that patients with bipolar II disorder are less likely to have antidepressant-induced manic/hypomanic switches than those with bipolar I disorder.[4,5] On the other hand, patients with bipolar II disorder may benefit more from lithium maintenance treatment than those with bipolar I disorder.[6]

Comorbid substance use disorder (SUD) in bipolar disorders is a rule, not an exception.[7-10] A higher rate of SUD in patients with bipolar I disorder than in those with bipolar II disorder was observed in the Epidemiologic Catchment Area (ECA) study[7] and some clinical studies[11,12] There are studies comparing the historical correlates and/or comorbidities between the 2 subtypes.[11,13-20] However, there has never been a study comparing the clinical correlates in patients with bipolar I disorder or bipolar II disorder and a recent history of SUD. Such information is important and can be useful for future research and clinical management in this subgroup of patients with bipolar disorder. Therefore, this study utilized a dataset at initial assessment of patients with rapid-cycling bipolar I or II disorder and a recent history of SUD who participated in 2 similar clinical trials to compare clinical variables according to the subtypes, rapid-cycling bipolar I disorder versus rapid-cycling bipolar II disorder.

Method

Patient Population

Cross-sectional data of a cohort of patients with rapid-cycling bipolar disorder who were recruited for 2 randomized, double-blind, placebo-controlled clinical trials were analyzed retrospectively. (The www.clinicaltrials.gov identifiers were NCT00194129 for study 1 and NCT00221975 for study 2.) The studies were conducted from November 1997 to February 2007 at the Bipolar Disorder Research Center of the Mood Disorders Program at University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio. The studies were conducted to assess the efficacy of different regimens for managing the acute and maintenance treatment of rapid-cycling bipolar disorder accompanied by a “recent” history of SUD. Patients who had a diagnosis of substance dependence and continued to meet abuse or dependence criteria for 1 or more substances in the past 6 months at the initial assessment (study 1 and study 2) or those who had a diagnosis of substance abuse and had continued abusing a substance in the last 3 months (study 1) or 6 months (study 2) were considered to have a recent history of SUD. The patients were referred from specialty clinics, private and public mental health centers, and advertisements. The respective institutional review boards' approval was obtained, and patients provided written, informed consent for each study. The study designs, study index, inclusion and exclusion criteria, and stages of the 2 studies at the time of this analysis are summarized in Table 1.

Initial Assessments

Diagnoses of rapid-cycling bipolar disorder, anxiety disorders (including generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder), SUDs, and other DSM-IV Axis I disorders were ascertained by extensive clinical interview (ECI) and the Mini-International Neuropsychiatric Interview (MINI)[21] by research psychiatrists and research assistants. The ECI, which is similar to the Structured Clinical Interview for the DSM-IV, Patient Edition (SCID-P),[22] consists of questions and criteria for the diagnosis of DSM-IV Axis I disorders but also contains items to assess mental status, severity of suicidality, demographics, and other variables of interest. The ECI and the MINI combination typically included a 60- to 90-minute initial interview done by a Master's level research assistant and a 30- to 45-minute second evaluation carried out by a research psychiatrist who confirmed bipolar diagnosis, a recent history of substance use disorder, and other findings from the first visit. A certified research assistant administered the MINI at the third visit lo confirm and expand the diagnoses of other Axis I disorders. For the MINI certification, a minimal κ of 0.8 on 10 cases rating against a leading rater who was certified by the Systematic Treatment Enhancement Program for Bipolar Disorder[23] was required. The agreement between the ECI and the MINI diagnosis was over 90%. If any inconsistency occurred with the first and second evaluations during the MINI administration, a psychiatrist would reevaluate the patient. For the diagnosis of substance use disorders, the SCID-P was used instead of the MINI at the third visit.

The severity of SUDs was assessed with the Addiction Severity Index (ASI),[24] which is designed to detect and measure the severity of potential treatment problems; the ASI focuses

on the past 30 days in 7 areas commonly affected by alcohol and drug dependence, including medical, employment, alcohol, drugs, legal, family/social, and psychiatric problems. Overall function and health conditions were assessed with the Global Assessment Scale (GAS)[25] and the Medical Outcomes Study 36-Item Short-Form Health Survey-36 (SF-36).[26] The SF-36 is a multi-purpose, short-form health survey with 36 questions that assess functional status (physical functioning, social functioning, role limitations-physical and emotional problems), well-being (mental health, vitality, and pain), and overall evaluation of health (general health perception and health change). Collateral information from the mandatory presence of a patient's significant other(s) was required in all cases during the initial assessment. Patients who met anxiety disorder criteria prior to or at the time of initial assessment were considered to have a lifetime history of anxiety disorder. Patients who met substance abuse or dependence criteria prior to or at the initial assessment were considered to have a lifetime history of SUD.

Procedures

Data from the initial assessment of the 2 studies were merged into one dataset and analyzed based on bipolar subtypes, rapid-cycling bipolar I disorder versus rapid-cycling bipolar II disorder. Historical variables, including health insurance status, comorbid anxiety disorders and SUDs, previous history of hospitalization, suicide attempt, or early childhood abuse, and recent clinical variables, including ASI composite scores, GAS scores, SF-36 physical and mental component scores, and numbers of episodes in the last 12 months, were compared. Any SUD meant the presence of alcohol or drug (legal or illegal) abuse or dependence except for caffeine and nicotine. Any anxiety disorder meant the presence of generalized anxiety disorder, panic disorder, and/or obsessive-compulsive disorder.

Statistical Analysis

All analyses were based on the assumption that the data were normally distributed. The hypotheses were that patients with bipolar I disorder would have higher rates or scores of these clinical variables than would those with bipolar II disorder. Analysis of variance was used to analyze the continuous variables and standard deviation was used to reflect the magnitude of variance. For categorical data, χ^2 tests were used for significance testing. Odds ratios were used for risk estimate and are presented with CIs. Given the exploratory nature of the study, statistical significance was set at $\alpha = .05$, 2-tailed, in order to detect potentially clinically meaningful associations. The 95% CI presents with the mean ± 1.96 SE. Because multiple comparisons occurred, a simple Bonferroni adjustment was applied. Accordingly, the adjusted p value for each comparison equals .05/45 = 0.0011.

Results

Demographics and Lifetime Clinical Correlates

As shown in Table 2, at the initial assessment there was no difference in the mean age at study entry, sex, or insurance status between those with rapid-cycling bipolar I disorder and rapid-cycling bipolar II disorder. In terms of the number of lifetime comorbid Axis I disorders, significantly fewer patients with rapid-cycling bipolar I disorder had only 1 comorbid disorder than those with rapid-cycling bipolar II (6.8% vs. 20.4%, p = .003) before

Bonferroni adjustment. However, patients with rapid-cycling bipolar I had significantly higher rates of any comorbid anxiety disorder (62.3% vs. 38.9%, p = .0021), generalized anxiety disorder (52.4% vs. 27.8%, p = .0013), and panic disorder (39.3% vs. 14.8%, p = .0008) than those with rapid-cycling bipolar II disorder before Bonferroni adjustment. Moreover, only the difference in panic disorder was still significant after adjustment for multiple comparisons. There were no significant differences between bipolar subtypes, in the rates of lifetime history of hospitalization, suicide attempt, or substance use disorders, as a group or individually, in rates of early childhood abuse or the number of lifetime substance use disorders.

Severity Measurements at the Initial Assessment

As shown in Table 3, among the ASI composite scores of the 7 areas, only mean ± SD psychiatric subscores were significantly different between the 2 subtypes even after the Bonferroni adjustment (0.59 ± 0.14 vs. 0.51 ± 0.15, p = .0007). In terms of the number of mood episodes over the past 12 months, there was no significant difference between the 2 subtypes in mania/hypomania, depression, or total episodes. Both groups also had a similar GAS score indicative of a moderate impairment in global functioning.

For the SF-36 analysis, there were only 99 patients available (rapid-cycling bipolar I disorder, N = 85, rapid-cycling bipolar II disorder, N = 14). Mean ± SD physical component scores were significantly lower in patients with rapid-cycling bipolar I disorder, 56.8 ± 15.2 than those with rapid-cycling bipolar II disorder, 65.4 ± 13.9 (95% CI = −15.0 to −2.1, p = .013). There was no significant difference in the mean ± SD mental component scores, 36.7 ± 13.6 versus 38.5 ± 17.8 (95% CI =−10.5 to 4.9, p = .483).

Discussion

In patients with rapid-cycling bipolar disorder and a recent history of SUD, we found that those with rapid-cycling bipolar I disorder and those with rapid-cycling bipolar II disorder had more similarities than differences in terms of lifetime historical correlates, severity of recent SUDs, global functioning, and overall health conditions. However, the rate of comorbid panic disorder and AS1 psychiatric composite scores in patients with rapid-cycling bipolar I differed significantly from those with rapid-cycling bipolar II. The AS1 psychiatric subscale covers severity of depression and anxiety; trouble understanding, concentrating, or remembering; violent behavior; thoughts of suicide or attempted suicide; experience of psychosis; or psychological or emotional problems in the past 30 days. The difference in SF-36 physical component (physical functioning, role-physical, bodily pain, and general health) scores also suggested that patients with rapid-cycling bipolar I disorder may have a more severe physical problem than those with rapid-cycling bipolar II disorder.

These findings are consistent with previous studies indicating that, while both bipolar subtypes are disabling disorders, and there are similarities between them, important differences do exist between the subtypes.[13-17] For instance, in a National Institute of Mental Health Collaborative Depression Study, Judd and colleagues[14] found that psychosocial impairment increases significantly with each increment in depressive symptom severity, with equal impairments across bipolar I disorder and bipolar II disorder. The

psychosocial impairment also significantly increases with increments in manic symptoms for bipolar I disorder. However, subsyndromal hypomanic symptoms are not disabling in bipolar II disorder and may even enhance functioning. Similarly, Maina and colleagues[15] reported that euthymic patients with bipolar disorder had lower mean scores on the SF-36 compared to those without a psychiatric disorder, similar to euthymic patients with major depressive disorder. However, in a subgroup analysis, bipolar II disorder was associated with poor health-related quality of life compared to those with bipolar I disorder during the sustained periods of euthymia. On the contrary, the same group of investigators observed that the negative impact of comorbid anxiety disorders on quality of life was restricted to those with bipolar I disorder but not to those with bipolar II disorder, which is consistent with our results.[16] Clearly, the relationship between quality of life and bipolar subtypes warrants further investigation with a larger group of patients.

The similar clinical presentations of patients with rapid-cycling bipolar I disorder and those with rapid-cycling bipolar II disorder in this study should not serve to deemphasize the differences between the subtypes. One such important area is the difference in SUD prevalence. The ECA study data showed that patients with bipolar I disorder had higher rates of SUD than those with bipolar II disorder.[7] Our previous analysis[27] in a larger sample of patients with rapid-cycling bipolar disorder also showed that patients with rapid-cycling bipolar I disorder had significantly higher rates of SUDs than those with rapid-cycling bipolar II disorder. Higher rates of comorbid SUDs in patients with bipolar I disorder (42%–78%) compared to those with bipolar II disorder (17%–48%) has been reported in other studies. [11,12,28,29]

The finding of similar levels of severity of SUD between these 2 groups of patients has a very important clinical implication. It is well known that the impairment in social, occupational, or other areas of functioning is universal to patients with SUDs. However, the magnitude of impairment often varies dramatically, mainly depending on the class and numbers of substances of abuse/dependence. In a study comparing women with posttraumatic stress disorder and comorbid cocaine or alcohol dependence, it was found that patients with cocaine dependence demonstrated greater social and occupational impairment, more legal problems, and more frequent partner violence compared to those with alcohol dependence.[30,31] It has also been reported that the severity of SUD intensifies as the number of different substances of abused/dependence increases.[32,33] Moreover, patients with polysubstance abuse/dependence are at increased risk for violence and legal complications as well as reduced work productivity.[34] The results from this study suggest that patients with bipolar II disorder and a recent history of SUD deserve attention equal to their bipolar I disorder counterparts.

The association between bipolar disorder and panic disorder has been reported by other investigators.[35-41] Family and genetic studies have shown that bipolar-panic comorbidity is heritable,[36-38] and comorbid panic disorder increases the risk for rapid mood switching.[35] It remains unclear whether this association is subtype specific. A numerical increase in the rate of panic disorder in patients with bipolar I disorder compared to those with bipolar II disorder was observed in some previous studies[11,20] but not in others.[19,42] Comorbid panic disorder may pose additional challenges for the treatment of bipolar disorder, as these

patients may be less responsive to conventional treatment and require a longer duration to achieve recovery.[43,44]

These findings must be considered in view of several methodological limitations. First, data obtained in this study were cross-sectional. Second, only the diagnosis of a lifetime anxiety disorder was available for analysis, and not all anxiety disorders were assessed. Third, depending on the recall of history by patients and significant others, the diagnoses and clinical correlates might not be accurate, although the required presence of significant others was intentionally used to minimize such potential inaccuracy. Fourth, our sample only included outpatients with rapid-cycling bipolar disorder and might be less generalizable to other bipolar populations. Despite these limitations, our study has strengths. First, to our knowledge, this is the first report in patients with rapid-cycling bipolar disorder to compare the clinical variables between subtypes. Second, our sample included only patients with a recent history of SUD, which other studies did not study or did not analyze.[7,11,18]

Conclusions

Patients with rapid-cycling bipolar I disorder and a recent history of SUD had more similarities to than differences from those with rapid-cycling bipolar II disorder and the same history. Therefore, they should be treated equally and seriously with a systematic multi-disciplined approach. The significantly higher rate of comorbid panic disorder in patients with rapid-cycling bipolar I disorder may add challenges for managing this subgroup of patients.

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Table 1

Studies of Patients With Rapid-Cycling Bipolar Disorder and Recent Substance Use Disorder

Study Information	Study 1 (N- 149)[a]	Study 2 (N = 96)[b]
Study design	Open-label stabilization with lithium + divalproex for up to 24 wk: protocol-defined responders receiving lithium + divalproex or lithium + placebo for 24 wk; a placebo-controlled discontinuation maintenance study	Open-label treatment with lithium + divalproex for up to 24 wk; protocol-defined nonresponders receiving lithium + divalproex + placebo or lithium + divalproex + lamotrigine for 6 wk; a placebo- controlled acute depression efficacy study
Mood state	Manic/hypomanic/mixed within 3 mo; any mood at screening/baseline	Major depressive episode at screening/baseline
Inclusion criteria	Bipolar I or II disorder, rapid cycling within last 12 mo, ≥ 16 y old; no contraindication to lithium or divalproex; substance abuse/dependence within last 6 mo	Bipolar I or II disorder, rapid cycling within last 12 mo. ≥ 16 y old; no contraindication to lithium, divalproex, or lamotrigine; substance abuse within 3 mo. dependence within 6 mo
Exclusion criteria	Contraindications to lithium levels of 0.8 mEq/L or divalproex levels of 50 μg/mL	Contraindications to lithium, divalproex, or lamotrigine
Data collection	November 1997 to September 2006; study was completed	July 2002 to February 2007; study was ongoing

[a] ClinicalTrials.gov identifier NCl00194I29.

[b] ClinicalTrials.gov identifier NCT00221975.

Table 2

Comparisons of Demographics and Historical Correlates Between Patients With RCBPI and RCBPII With a Recent History of Substance Use Disorder

Characteristic	RCBPI (N = 191)		RCBPII (N = 54)		RCBPI vs RCBPII		
	Mean	SD	Mean	SD	OR	Wald 95% CI	P
Age at study entry, y	36 N	9.9 %	35.3 N	10.4 %	…	…	.671
Sex							
Male	122	63.9	32	59.3	1.22	0.66 to 2.26	.5354
Female	69	36.1	22	40.7	…	…	…
Health insurance status at baseline							
None	90	47.1	29	53.7	1.08	0.61 to 1.90	.802
Commercial	71	37.4	22	40.7	0.86	0.46 to 1.60	.633
Medicaid/Medicare/Veterans Administration	29	15.3	5	9.3	1.75	0.64 to 4.78	.266
Lifetime comorbid Axis I disorders, no.[a]							
1	13	6.8	11	20.4	0.29	0.12 to 0.68	.003
2	36	18.9	12	22.2	0.81	0.39 to 1.70	.581
3	48	25,3	11	20.4	1.31	0.63 to 2.75	.470
4	40	21.1	7	13.0	1.78	0.75 to 4.23	.189
≥ 5	53	27.9	13	24.1	1.21	0.60 to 2.44	.591
Lifetime comorbid anxiety disorders							
Any	119	62.3	21	38.9	2.60	1.40 to 4.83	.0021
Generalized anxiety disorder	100	52.4	15	27.8	2.86	1.48 to 5.53	.0013
Panic disorder	75	39.3	8	14.8	3.72	1.66 to 8.32	.0008*
Obsessive-compulsive disorder	14	7.3	5	9.3	0.78	0.27 to 2.26	.6397
Lifetime history							
Hospitalization	135	71.4[c]	35	66.0[d]	1.31	0.69 to 2.48	.4089
Suicide attempt	90	47.6[c]	19	35.8[d]	1.64	0.88 to 3.07	.1191
Early childhood history							
Verbal abuse	90	50.3[c]	21	45.7[g]	1.40	0.76 to 2.59	.2833

Characteristic	RCBPI (N = 191)		RCBPII (N = 54)		RCBPI vs RCBPII		
	Mean	SD	Mean	SD	OR	Wald 95% CI	P
Physical abuse	70	38.9[f]	14	30.4[g]	1.65	0.84 to 3.25	.1427
Sexual abuse	47	26.3[e]	7	15.6[h]	2.19	0.93 to 5.18	.0683
Lifetime dependence							
Any	176	92.1	49	90.7	1.20	0.42 to 3.46	.739
Alcohol	131	69.3[c]	37	69.8[d]	1.00	0.52 to 1.92	.9924
Marijuana	63	33.7[i]	13	24.5[d]	1.55	0.78 to 3.10	.2113
Cocaine	74	39.6[i]	16	30.2[d]	1.50	0.78 to 2.89	.2199
Others[b]	32	16.8	7	13.0	1.35	0.56 to 3.26	.5013
Lifetime abuse							
Any	115	60.2	32	59.3	1.04	0.56 to 1.93	.8998
Alcohol	40	21.2[c]	12	22.6[d]	0.93	0.45 to 1.92	.839
Marijuana	55	29.4[i]	21	39.6[d]	0.64	0.34 to 1.19	.1568
Cocaine	29	15.5[i]	9	17.0[d]	0.90	0.40 to 2.03	.7903
Others[b]	53	27.7	13	24.1	1.21	0.60 to 2.44	.5909
Lifetime substance use disorders, no.							
1	43	22.6	16	29.6	0.69	0.35 to 1.34	.2801
2	41	21.6	13	24.1	0.86	0.42 to 1.76	.6831
3	60	31.6	9	16.7	2.29	1.05 to 4.99	.0333
≥ 4	46	24.2	16	29.6	0.75	0.39 to 1.48	.4078

[a] Including anxiety disorders and substance use disorders.

[b] Including stimulants, sedatives, opiates, and hallucinogens.

[c] Percentage based on N = 189.

[d] Percentage based on N = 53.

[e] Percentage based on N= 179.

[f] Percentage based on N = 180.

[g] Percentage based on N = 46.

[h] Percentage based on N = 45.

[i] Percentage based on N = 187.

[*] Still Significant after Bonferroni adjustment (.05/45); the adjusted p value = .0011.

Abbreviations: OR = odds ratio, RCBPI = rapid-cycling bipolar I disorder, RCBPII = rapid-cycling bipolar II disorder.

Symbol: … = not applicable.

Table 3

Comparisons of Clinical Variables at Initial Assessment Between Patients With RCBPI and RCBP1I and a Recent History of Substance Use Disorder

	RCD PI (N = 191)		RCBI (N = 54)		RCBPI vs RCBPII	
Variable	**Mean**	**SD**	**Mean**	**SD**	**Wald 95% CI**	**P**
Addiction Severity Index composite scores						
Medical	0.25	0.32	0.19	0.3	−0.03 to 0.15	.2044
Employment	0.46	0.29	0.41	0.27	−0.03 to 0.13	.2418
Alcohol	0.27	0.24	0.31	0.23	−0.11 to 0.13	.2677
Drug	0.09	0.1	0.09	0.09	−0.03 to 0.03	1.0000
Legal	0.1	0.18	0.12	0.21	−0.08 to 0.04	.5272
Family/social support	0.32	0.25	0.27	0.21	−0.02 to 0.12	.1415
Psychiatric	0.59	0.14	0.51	0.15	0.04 to 0.13	.0007*
Total	0.3	0.1	0.28	0.09	−0.01 to 0.05	.1614
Episodes in past 12 mo, no.						
Mania/hypomania	6.8	4.86	6.35	4.26	−0.88 to 1.78	.5075
Depression	6.91	5.72	6.41	4.27	−0.90 to 1.90	.4855
Total	13.71	10.12	12.76	8.51	−1.74 to 3.64	.4884
Global Assessment Scale scores	51.15	7.46	53.57	7.53	−4.69 to -0.15	.0405

*Still significant after Bonferroni adjustment (.05/45); the adjusted p value = .0011.

Abbreviations: RCBPI = rapid-cycling bipolar I disorder, RCBPII = rapid-cycling bipolar II disorder.