Correlates of Historical Suicide Attempt in Rapid-Cycling Bipolar Disorder: A Cross-Sectional Assessment

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Objective: A rapid-cycling course in bipolar disorder has previously been identified as a risk factor for attempted suicide. This study investigated factors associated with suicide attempts in patients with rapid-cycling bipolar I or II disorder.

Method: Cross-sectional data at the initial assessment of patients who were enrolled into 4 clinical trials were used to study the factors associated with suicide attempt. An extensive clinical interview and the Mini-International Neuropsychiatric Interview were used to ascertain DSM-IV diagnoses of rapid-cycling bipolar disorder, substance use disorders, anxiety disorders, psychosis, and other clinical variables. Chi-square, t test, and logistic regression or Poisson regression were used to analyze the data where appropriate, with odds ratios (ORs) for relative risk estimate. The data were collected from September 1995 to June 2005.

Results: In a univariate analysis, 41% of 561 patients had at least 1 lifetime suicide attempt. Earlier age of depression onset, bipolar I subtype, female sex, unmarried status, and a history of drug use disorder, panic disorder, sexual abuse, and psychosis were associated with significantly higher rates of attempted suicide (all $p < .05$). After considering 31 potential confounding factors in the stepwise logistic regression model (n = 387), any Axis I comorbidity (OR = 2.68, p = .0219), female sex (OR = 2.11, p = .0005), psychosis during depression (OR = 1.84, p = .0167), bipolar I subtype (OR = 1.83, p = .0074), and history of drug abuse (OR = 1.62, p = .0317) were independent predictors for increased risk of attempted suicide. However, white race was associated with a lower risk for suicide attempt (OR = 0.47, p = .0160). Psychosis during depression (p = .0003), bipolar I subtype (p = .0302), and physical abuse (p = .0195) were associated with increased numbers of suicide attempts by 248%, 166%, and 162%, respectively; white race was associated with a 60% decrease in the number of suicide attempts (p = .0320).

Conclusion: In this highly comorbid group of patients with rapid-cycling bipolar disorder, 41% had at least 1 suicide attempt. Among the demographics, female sex was positively associated, but white race was negatively associated, with the risk for suicide attempt. Independent clinical variables for increased risk and/or number of attempted suicides were any Axis I comorbidity, psychosis during depression, bipolar I subtype, a history of drug abuse, and physical abuse.

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A rapid-cycling course in bipolar disorder has been identified as a risk factor for attempted suicide in the majority of previous studies.[1–10] A recent meta-analysis showed that patients with rapid cycling were 54% more likely to attempt suicide compared to those without rapid cycling.[11] More importantly, in the Collaborative Depression Study sponsored by the National Institute of Mental Health (NIMH), Coryell et al.[6] found that bipolar patients with a rapid-cycling course prior to study entry had significantly higher rates of attempted suicide, attempts of high intent, and attempts in high lethality compared to those without rapid-cycling bipolar disorder. The significantly increased risk for suicide attempt in those with rapid-cycling bipolar disorder held true during a 2-year follow-up period despite the majority of those patients no longer meeting criteria for rapid cycling.[6]

The prevalence of patients with current rapid-cycling bipolar disorder has been reported to be 13% to 56%.[12,13] A recent meta-analysis of 2054 bipolar patients from 8 studies that included inpatients or outpatients without a priori selection of rapid cyclers and without matching the numbers of rapid cyclers to non–rapid cyclers found that 16.3% of patients met the criteria of rapid-cycling bipolar disorder.[14] However, there has never been a study on the risk factors associated with suicide attempts in a cohort of patients solely with rapid-cycling bipolar disorder. In the recent meta-analysis by Hawton and colleagues,[11] single marital status, a family history of suicide, hospital admission because of depression, mixed state, comorbid anxiety disorder, and alcohol and/or drug abuse, but not gender, bipolar subtype,

or married or unemployed status, were associated with an increased risk for nonfatal suicidal behavior.

In a large outpatient study of the Stanley Foundation Bipolar Network, Leverich and colleagues[15] found that both physical and sexual abuse in early childhood were associated with an increased risk for suicide attempt.[15] Differences between patients with rapid-cycling bipolar disorder and those without in clinical course, comorbidities, and treatment responses have been reported.[5,6,8,16,17] It remains unclear whether those factors associated with the increased risk for suicide attempt in non–rapid cycling or mixed populations are also applicable to patients with rapid-cycling bipolar disorder.

In addition, a higher lethality of suicide attempts in bipolar disorder than in the general population has been reported, as demonstrated by a ratio of 3:1 (suicide attempts:completed suicides) in bipolar disorder versus 30:1 in the general population.[18] A higher lethality in patients with bipolar II disorder than in those with major depressive disorder was also found in a more recent study of suicidal behaviors in 2826 patients with mood disorders.[19] Clearly, to identify factors associated with the increased risk for suicide attempt in patients with rapid-cycling bipolar disorder is imperative. Therefore, we proposed to use the cross-sectional data of a cohort of patients with rapid-cycling bipolar disorder to study the independent predictors of a past suicide attempt.

METHOD

Patient Population

Cross-sectional data of a cohort of patients with rapid-cycling bipolar disorder who were recruited for 3 NIMH-funded and 1 Stanley Medical Research Institute–funded randomized, double-blind, placebo-controlled clinical trials were used. Efficacy data of 2 trials have been published[20,21] and for the other 2 are under preparation (www.clinicaltrials.gov Identifiers NCT00221975 and NCT00063362). These studies were conducted at the Mood Disorders Program of Case Western Reserve University/University Hospitals Case Medical Center (Cleveland, Ohio) to assess the efficacy of different pharmacologic regimens for managing the acute and maintenance treatment of rapid-cycling bipolar disorder with or without a recent history of substance use disorder (SUD). The data were collected from September 1995 to June 2005.

All patients were treated with divalproex and lithium initially in an open-label phase. A *recent* SUD was defined as having a DSM-IV diagnosis of substance dependence and continuing to meet abuse or dependence criteria for a substance(s) in the last 6 months at the time of initial assessment or having a DSM-IV diagnosis of substance abuse and continuing to abuse a substance(s) in the previous 3–6 months. Men and women at least 16 years of age were eligible for these studies if they met DSM-IV criteria for (1) bipolar disorder I or II and (2) rapid cycling within the last 12 months (≥ 4 episodes in the last 12 months). The inclusion and exclusion criteria and baseline mood states of patients included in these studies are summarized in Table 1. Patients were referred from a variety of settings, including specialty clinics and private and public mental health centers, and were recruited through advertisement. The respective institutional review board approval was obtained and patients provided written, informed consent.

Initial Assessments

The procedures for the initial assessment have also been described in detail previously.[21–23] Briefly, the diagnoses of rapid-cycling bipolar disorder; anxiety disorders, including generalized anxiety disorder (GAD), panic disorder, and obsessive-compulsive disorder (OCD); SUDs; and other DSM-IV Axis I disorders, including history of psychosis during mania or depression, were ascertained by extensive clinical interview alone (n = 391)[20] and with the Mini-International Neuropsychiatric Interview (MINI)[24] by research psychiatrists and research assistants. For the diagnosis of SUDs, the Structured Clinical Interview for the DSM-IV, Patient Edition (SCID-P)[25] was used instead of the MINI. The extensive clinical interview not only consists of questions and criteria for the diagnosis of DSM-IV Axis I disorders, which is similar to the SCID-P, but also contains items to assess mental status, previous suicide attempt(s), demographics, and other variables of interest. During the MINI administration, if any inconsistency occurred with the diagnostic findings of the extensive clinical interview, a psychiatrist would reevaluate the patient until a consensus was reached. Collateral information from the mandatory presence of a patient's significant other(s) was required in all cases during the initial assessment.

The age at onset of first manic/hypomanic and depressive episode was retrospectively determined after the criteria for each of these episodes was explained to patients. The number of episodes of manic/hypomanic and depressive episodes in last 12 months was directly inquired. Each patient must have had ≥ 4 DSM-IV–defined episodes of a major depressive, manic, mixed, or hypomanic episode and must have been demarcated by either a period of full remission or by a switch to an episode of the opposite polarity. However, in patients who also had episodes that only met the symptom criteria, but not the duration, and switched to an episode of the opposite polarity, these episodes were counted into the total episodes in the last 12 months.

The time to first mood stabilizer treatment was determined by the time from first onset of mania/hypomania to the first time of a mood stabilizer treatment or electroconvulsive therapy for manic or hypomanic symptoms. The mood stabilizers for mania/hypomania were defined as lithium, divalproex/valproic acid, carbamazepine, and typical and atypical antipsychotics.

Experience of early life trauma was inquired about with the question, "Have you ever been physically, verbally, or

Table 1. Inclusion and Exclusion Criteria of 4 Studies and the Baseline Demographics and Mood States of Patients With Rapid-Cycling Bipolar Disorder Included in the Studies

	Without Recent History of Substance Use Disorder		With Recent History of Substance Use Disorder	
Variable	Study I (n = 254)[a]	Study II (n = 110)[b]	Study III (n = 137)[c]	Study IV (n = 66)[b]
Inclusion criteria	Bipolar I or II disorder Rapid cycling in last 12 mo ≥18 years old No contraindication to lithium or valproic acid	Bipolar I or II disorder Rapid cycling in last 12 mo ≥16 years old No contraindication to lithium, valproic acid, or lamotrigine	Bipolar I or II disorder Rapid cycling in last 12 mo ≥16 years old No contraindication to lithium or valproic acid Substance use disorder in 6 mo	Bipolar I or II disorder Rapid cycling in last 12 mo ≥16 years old No contraindication to lithium, valproic acid, or lamotrigine Substance abuse in 3 mo Substance dependence in 6 mo
Exclusion criteria	Contraindication to lithium or valproic acid Substance use disorder in 6 mo	Contraindication to lithium, valproic acid, or lamotrigine Substance abuse in 3 mo Substance dependence in 6 mo	Contraindication to lithium or valproic acid	Contraindication to lithium, valproic acid, or lamotrigine
Age at study entry, mean (SD), y	36.8 (10.5)	37.7 (9.8)	36.0 (10.1)	34.1 (9.5)
Sex, n (%)				
Male	92 (36.2)	46 (41.8)	86 (62.8)	43 (65.2)
Female	162 (63.8)	64 (58.2)	51 (37.2)	23 (34.8)
Race, n (%)				
White	220 (86.6)	101 (91.8)	114 (83.2)	62 (93.9)
Nonwhite	34 (13.4)	9 (8.2)	23 (16.8)	4 (6.1)
Marital status, n (%)				
Married	97 (38.2)	40 (36.4)	24 (17.5)	13 (19.7)
Separated/divorced	63 (24.3)	21 (19.1)	48 (35.0)	21 (31.8)
Widowed	3 (1.2)	2 (1.8)	3 (2.2)	1 (1.5)
Never married	91 (35.8)	47 (42.7)	62 (45.3)	31 (47.0)
Mood states at baseline, n (%)				
Depressed	142 (55.9)	110 (100.0)	65 (47.4)	66 (100.0)
Hypomanic	68 (26.8)	NA	26 (19.0)	NA
Manic	12 (4.7)	NA	23 (16.8)	NA
Mixed	7 (2.8)	NA	19 (13.9)	NA
Euthymic	17 (6.7)	NA	4 (2.9)	NA
Attempted suicide, n (%)	97 (38.2)	43 (39.1)	64 (46.7)	27 (40.9)

[a]Calabrese et al.[20]
[b]www.clinicaltrials.gov Identifier NCT00063362 (study II) and NCT00221975 (study IV).
[c]Kemp et al.[21]
Abbreviation: NA = not applicable.

sexually abused?" If a patient answered yes, then the patient was asked how and when the abuse occurred and who the perpetrator(s) was. No attempt was made to assess the severity of abuse. Trauma that occurred during childhood or adolescence was included in the analysis. Other historical variables were also collected during the initial assessment.

Suicidal thinking was assessed at baseline and at each visit to assure the safety of patients during the study period. The past history of suicide attempt(s) was assessed by directly asking patients, "Have you ever attempted suicide?" If a patient answered yes, then the patient was asked when the suicide attempt occurred, how the suicide attempt was carried out—such as overdose on medication, cutting, hanging or other means—and what the consequence of the suicide attempt was—such as pumping stomach, suturing wound, coma, hospitalization, etc. No attempt was made to differentiate intentional from accidental acts.[26] However, for patients who had minor repeated self-injurious behaviors such as superficial cutting, but denied having any intent of suicide attempt(s), these acts would not be counted for suicide attempt. As other variables, the collateral information from significant other(s) was also taken into consideration during the assessment of previous suicide attempt.

Procedures

In order to have a larger sample, data from the initial assessment of the 4 studies were used. Because in one study[20] and in the early phase of another study[21] not all anxiety disorders or other Axis I disorders were assessed, history of social phobia and posttraumatic stress disorder were not available for the analyses. Data were organized according to a history of suicide attempt. To assess the overall suicide attempt in this population, the frequency of suicide attempt(s) was calculated and followed by comparisons of variables of interest between those with and without a history of suicide attempt. These variables covered the demographics, bipolar subtypes, severity and courses of bipolar illness, and comorbid psychiatric disorders (see Statistical Analysis). Lifetime any anxiety disorder meant the presence of GAD, panic disorder, and/or OCD. Lifetime any SUD meant the

presence of alcohol or drug (legal or illegal) abuse or dependence with the exception of nicotine and caffeine. Lifetime any comorbidity meant the presence of GAD, panic disorder, OCD, alcohol abuse/dependence, and/or drug abuse/dependence.

Statistical Analysis

Univariate analyses were carried out to compare the differences between patients with and without a history of attempted suicide. A univariate analysis was performed to provide a comparison with prior studies using this analysis. Stepwise logistic regression was used to identify independent predictors of the probability for suicide attempt. Poisson regression was used to identify independent predictors of the expected number of suicide attempts. The increase or decrease in the expected number of suicide attempts was calculated by 100 [exp (coefficient) –1], where "coefficient" refers to the regression coefficient of the relevant predictor. To evaluate continuous variables, t tests were used, with standard deviation to reflect the magnitude of variance. Chi-square tests were used to evaluate categorical data, with odds ratio (OR) for risk estimate and 95% confidence interval (CI) to reflect the magnitude of variances. Given the exploratory nature of the study, statistical significance was set at $\alpha = .05$, 2-tailed, in order to detect potentially clinically meaningful associations. Therefore, no adjustment for multiple comparisons was made.

For the regression analysis, the following 31 variables were considered as predictors in the model: demographics, including the age at study entry, gender, race (white vs. nonwhite), and marital status (married vs. not married); bipolar subtypes (bipolar I vs. bipolar II); mania/hypomania related variables, including the age at onset of first mania/hypomania, manic/hypomanic episodes in the last 12 months, a lifetime history of psychosis during manic episodes, and the time to first mood stabilizer treatment for manic/hypomanic symptoms; depression-related variables, including the age at onset of first depressive episode, depressive episodes in the last 12 months, and a lifetime history of psychosis during depression; variables of co-occurring DSM-IV Axis I disorders, including alcohol use disorders (abuse or dependence), drug use disorders (abuse or dependence), substance use disorders (alcohol and/or drug), and anxiety disorders (GAD, OCD, panic disorder, GAD + panic disorder, or any anxiety disorder); variables reflecting overall severity (psychosis during mania and/or depression and any comorbidity—any anxiety disorder and/or any SUD); history of early life trauma (physical, verbal, or sexual abuse), and 4 studies.

RESULTS

Baseline Demographics, Mood States, and Number of Episodes in Last 12 Months

As shown in Table 1, in the 2 studies with a recent history of SUDs, patients were relatively younger, more likely to be male, and less likely to be married compared to those enrolled into the 2 studies without a recent history of SUDs. However, the mood states and rates of previous attempted suicide were similar. Data on the number of episodes in the last 12 months were not available in 42 patients. Among the rest of the patients, the number of episodes in the last 12 months was as follows: 4 (18%), 5–6 (17%), 7–8 (13%), 9–10 (5%), 11–12 (19%), 13–16 (5%), 17–20 (4%), and 23–24 (19%).

Distribution of the Number of Previous Suicide Attempts

Of 568 patients with rapid-cycling bipolar disorder, 561 had data regarding the presence or absence of a previous suicide attempt and 41.2% of them had at least 1 previous suicide attempt. Among those with history of attempted suicide, the number of previous suicide attempts varied from 1 time (47.2%), 2 times (29.4%), 3 times (10.8%), 4 times (4.3%), 5 times (2.6%), and ≥ 6 times (5.6%).

Clinical Correlates of Patients With or Without Suicide Attempt

As demonstrated in Table 2, among the continuous variables, only an early onset of depressive episode was significantly associated with an increased rate of suicide attempt. Among the categorical variables, female sex (OR = 1.7, 95% CI = 1.23 to 2.43), not being married (OR = 1.5, 95% CI = 1.04 to 2.24), bipolar I subtype (OR = 1.8, 95% CI = 1.29 to 2.57), and a lifetime history of drug use disorder (OR = 1.5, 95% CI = 1.08 to 2.12), drug abuse (OR = 1.6, 95% CI = 1.09 to 2.20), panic disorder (OR = 1.5, 95% CI = 1.02 to 2.15), sexual abuse (OR = 2.1, 95% CI = 1.39 to 3.17), overall psychosis (OR = 1.9, 95% CI = 1.35 to 2.67), psychosis during depression (OR = 2.77, 95% CI = 1.82 to 4.11), or psychosis during mania (OR = 1.66, 95% CI = 1.17 to 2.36) were associated with increased rates of suicide attempt.

Higher risk for suicide attempt in female patients was present in both bipolar subtypes. In patients with rapid-cycling bipolar I disorder, female patients had a significantly higher rate (84/150) of attempted suicide than male patients (67/169), with an OR of 1.9 (95% CI = 1.24 to 3.03, p = .0034). In patients with rapid-cycling bipolar II disorder, female patients also had a significantly higher rate (57/148) of attempted suicide than male patients (23/94), with an OR of 1.9 (95% CI = 1.09 to 3.44, p = .023).

Independent Predictors for the Probability of Suicide Attempt

Of the 561 patients, 387 had complete data on all 31 candidate variables and were eligible for stepwise logistic regression (probability) analysis. The independent predictors for attempted suicide (Table 3) were any Axis I comorbidity (OR = 2.68, 95% CI = 1.15 to 6.23), female sex (OR = 2.11, 95% CI = 1.38 to 3.22), psychosis during

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Table 2. Clinical Correlates of Patients With Rapid-Cycling Bipolar Disorder by History of Attempted Suicide

	Attempted Suicide (n = 231)		No Attempted Suicide (n = 330)		Attempted vs No Attempted 1-Way ANOVA	
Variable	Mean	SD	Mean	SD	Wald 95% CI	p
Age, y						
Entered the study	35.7	10.7	37	10.2	−3.07 to 0.47	.1495
First depression	13.2	6	14.5	6.9	−2.37 to −0.23	.0179
First mania/hypomania	15.9	6.7	16.6	7.5	−1.88 to 0.48	.247
Episodes in last 12 months						
Overall	11	7	11.7	7.1	−1.88 to 0.48	.2468
Depressive	6.3	9.6	7.6	13.3	−3.20 to 0.60	.1795
Manic/hypomanic	6.4	9.6	7.7	13.1	−3.18 to 0.58	.1755
Time to mood stabilizer treatment	15.7	10.9	17.5	11.6	−3.68 to 0.08	.0613
					χ^2 Test	
	N	%	N	%	OR (Wald 95% CI)	Pearson p
Study						
1	97	42.0	152	46.1	0.9 (0.60 to 1.19)	.3397
2	43	18.6	68	20.6	0.9 (0.56 to 1.35)	.5601
3	64	27.7	71	21.5	1.4 (0.95 to 2.06)	.0914
4	27	11.7	39	11.8	1.0 (0.59 to 1.66)	.9625
Sex						
Male	90	39.0	173	52.4		
Female	141	61.0	157	47.6	1.7 (1.23 to 2.43)	.0016
Race						
White	168	72.7	260	78.8		
Nonwhite	63	27.3	70	21.2	1.4 (0.94 to 2.06)	.0967
Marital status						
Married	54	23.4	105	31.8		
Not married	177	76.6	225	68.2	1.5 (1.04 to 2.24)	.0290
Bipolar subtype						
Bipolar I disorder	151	65.4	168	50.9	1.8 (1.29 to 2.57)	.0006
Bipolar II disorder	80	34.6	162	49.1		
Lifetime comorbid SUD						
Any SUD	165	71.4	208	63.0	1.3 (0.92 to 1.90)	.1359
Alcohol use disorder	144	62.3	186	56.4	1.2 (0.83 to 1.66)	.3609
Alcohol abuse	59	25.5	70	21.2	1.3 (0.86 to 1.89)	.2304
Alcohol dependence	84	36.4	111	33.6	1.1 (0.79 to 1.60)	.5043
Drug use disorder	130	56.3	146	44.2	1.5 (1.08 to 2.12)	.0165
Drug abuse	97	42.0	105	31.8	1.6 (1.09 to 2.20)	.0134
Drug dependence	63	27.3	75	22.7	1.3 (0.87 to 1.88)	.2185
Lifetime comorbid anxiety disorder						
Any anxiety disorder	116	50.4 (116/230)	145	44.3 (145/327)	1.3 (0.91 to 1.79)	.1559
GAD	85	37.1 (85/229)	114	34.8 (114/328)	1.1 (0.78 to 1.57)	.5670
Panic disorder	75	32.6 (75/230)	81	24.6 (81/329)	1.5 (1.02 to 2.15)	.0382
OCD	14	6.1 (14/230)	27	8.3 (27/325)	0.7 (0.37 to 1.40)	.3244
Early childhood abuse						
Verbal	107	54.3 (107/197)	136	45.9 (136/296)	1.4 (0.97 to 2.01)	.0686
Physical	75	38.1 (75/197)	90	30.3 (90/297)	1.4 (0.97 to 2.07)	.0730
Sexual	67	34.4 (67/195)	59	19.9 (59/296)	2.1 (1.39 to 3.17)	.0003
Previous psychotic symptoms						
Overall	121	52.6 (121/230)	121	36.9 (121/328)	1.9 (1.35 to 2.67)	.0002
During depression	71	30.70	45	13.8 (45/326)	2.77 (1.82 to 4.11)	< .0001
During mania	101	43.7	105	32.2 (105/326)	1.66 (1.17 to 2.36)	.0041

Abbreviations: ANOVA = analysis of variance, GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder, SUD = substance use disorder.

depression (OR = 1.84, 95% CI = 1.12 to 3.03), bipolar I subtype (OR = 1.83, 95% CI = 1.18 to 2.85), and a history of drug abuse (OR = 1.62, 95% CI = 1.04 to 2.50). However, white race was independently associated with a decreased risk for suicide attempt (OR = 0.47, 95% CI = 0.26 to 0.87).

Independent Predictors for the Number of Suicide Attempts

Of 387 patients with all 31 candidate variables, Poisson regression (count) analysis was also performed to identify independent predictors for the increased or decreased number of suicide attempts. Among these variables, psychosis during depression, bipolar I subtype, and history of physical abuse were independently associated with increased numbers of suicide attempts (Table 4). Respectively, the expected number of suicide attempts was increased by 248%, 166%, and 162% as calculated with 100 [exp (coefficient) −1]. Similar to the suicide probability analysis, white race was independently associated with decreased number of suicide attempts, a 60% decrease compared to nonwhite race (Table 4).

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Table 3. Predictors of the Probability for Attempted Suicide in Patients With Rapid-Cycling Bipolar Disorder

Predictor	Estimate	SE	p Value	OR	95% CI
Any comorbidity	0.9859	0.4302	.0219	2.68	1.15 to 6.23
Female sex	0.7463	0.2158	.0005	2.11	1.38 to 3.22
Psychosis during depression	0.6088	0.2544	.0167	1.84	1.12 to 3.03
Bipolar I disorder	0.6047	0.2258	.0074	1.83	1.18 to 2.85
History of drug abuse	0.4795	0.2232	.0317	1.62	1.04 to 2.50
White race	–0.7482	0.3106	.0160	0.47	0.26 to 0.87

Table 4. Predictors of the Number of Suicide Attempts in Patients With Rapid-Cycling Bipolar Disorder

Predictor	Estimate	SE	p Value	% Change
Psychosis during depression	0.9097	0.2503	.0003	248
Bipolar I disorder	0.5064	0.2336	.0302	166
History of physical abuse	0.4806	0.2054	.0195	162
White race	–0.5082	0.237	.032	–60

DISCUSSION

In this highly comorbid group of patients with rapid-cycling bipolar disorder in the last 12 months, more than 41% of patients had at least 1 suicide attempt, which is consistent with other studies of patients with rapid-cycling bipolar disorder, in which a history of attempted suicide ranges from 36% to 57%.[2,5,6,9] A history of any comorbidity, psychosis during depression, and drug use disorder; female sex; and bipolar I subtype were independent predictors of increased probability for attempted suicide. A history of psychosis during depression and physical abuse and bipolar I subtype were independent predictors of an increased number (from 162% to 248%) of attempted suicides. On the other hand, white race was not only independently associated with decreased risk for suicide attempt, but also associated with a decreased number of suicide attempts.

The findings of any comorbidity and history of drug abuse being independently associated with increased risk for suicide attempt are consistent with some previous studies.[11,15] The finding that alcohol use disorder was not an independent predictor is also consistent with some previous studies,[4,9,10,27–29] although others have reported that alcohol dependence is associated with increased risk for suicide attempt.[29,30] This discrepancy is more likely due to the differences in patient populations. In our study, both patients with and without suicide attempt had high rates of alcohol use disorders so that a "ceiling" effect of alcohol use disorders on suicide attempts in both groups might occur. Similarly, drug dependence did not have differential effect in these 2 groups (Table 2).

Although the comorbidity of anxiety disorders in bipolar disorder is a rule rather than an exception,[31,32] the independent impact of anxiety disorders on suicidality of patients with bipolar disorder remains unclear. In our study, only panic disorder was associated with an increased risk for suicide attempt in the univariate analysis. The disappearance of independent association of panic disorder with increased risk for attempted suicide after controlling for other variables suggests that panic disorder was highly correlated to bipolar subtypes in patients with rapid-cycling bipolar disorder. This bipolar-panic connection has also been reported in families with bipolar rapid mood switching.[16,17]

Many, but not all, studies have reported an association between comorbid anxiety disorders and increased suicide attempts.[4,10,11,29,33–40] This discrepancy is more likely due to differences in selection criteria and statistical methodologies (univariate analysis vs. regression analysis). For example, in their univariate analysis, Simon and colleagues[34] found that a history of any lifetime anxiety disorder and agoraphobia, but not each individual anxiety disorder, were associated with an increased risk of suicide attempt in patients with bipolar disorder. However, after controlling for age, gender, and SUD, only the any anxiety disorder category was still significant. After further controlling for bipolar severity (recovery status and the age of first mood episode), none of the anxiety disorder–related variables was associated with an increased risk for suicide attempt. Similarly, in an inpatient sample, Perroud et al.[29] found that only social phobia, but not other anxiety disorders, was an independent predictor for suicide attempt after controlling for potential confounding factors, although alcohol dependence, any anxiety disorder, agoraphobia, and GAD were significantly higher in those who attempted suicide than in those who did not in the univariate analysis. These 2 examples and our study suggest different statistical methodologies used in different studies may also explain some of the inconsistencies of previous findings in nonbipolar or mixed populations.[41–48]

Among the variables reflecting the severity and courses of bipolar illness, only psychosis during depression was independently associated with the increased risk and number of suicide attempts. Most previous studies have shown that variables related to depression severity[10,11,28,49–52] were associated with increased risk for suicide attempt. The association between a history of psychosis and an increased risk for suicide attempt has been reported in some studies,[53,54] but not in others.[27,36,41,55] One possible reason for such inconsistency might be due to different definitions of psychosis used in different studies, such as overall history of psychosis, psychosis during mania, or psychosis during depression. In our univariate analysis, all of these variables were significantly higher in those with suicide attempt than in those without (Table 2). However, in the logistic regression analysis, only psychosis during depression was still significantly associated with increased risk of suicide attempt.

The impact of early childhood trauma on the risk of suicide attempt in patients with rapid-cycling bipolar

disorder is consistent with the findings from a study of the Stanley Foundation Bipolar Network,[15] in which a history of early physical and sexual abuse was associated with significantly increased risk for suicide attempt. However, the disappearance of independent association between sexual abuse and increased risk for suicide attempt was unexpected, and might be due to controlling for bipolar subtypes and other variables in the regression analysis. In our previous study,[23] patients with rapid-cycling bipolar I disorder and a recent history of SUD had an increased rate of sexual abuse compared with their rapid-cycling bipolar II disorder counterparts.

The independent association of female sex and bipolar I subtype with the increased risk for suicide attempt is inconsistent with the findings of a recent meta-analysis.[11] However, a more recent study showed that patients with bipolar I disorder had higher rates of suicide attempt than their bipolar II disorder counterparts, but patients with bipolar II disorder had a higher lethality of suicide attempts than bipolar I patients, with a ratio of suicide attempts:completed suicide of 5.12:10.8.[19] On the other hand, a higher rate of suicide attempt in patients with bipolar II disorder than in those with bipolar I disorder has also been reported.[56,57] Other studies have reported no difference between bipolar I and II disorders in the rates of suicide attempt.[5,28] In these previously mentioned studies, potential confounding factors were not controlled. In terms of gender, the result from our study is consistent with the findings of Tondo et al.,[58] who reported the rate of suicide attempts in women was about double that for men. The negative association of white race with the risk for suicide attempt is consistent with a bipolar disorder registry study,[59] in which African American participants had a significantly higher rate of suicide attempt than whites.

One of the challenges in understanding factors that predict suicide attempts in patients with bipolar disorder is the large number of co-occurring psychiatric diagnoses often found in the same individual. In a recent report of the National Comorbidity Survey Replication, Merikangas and colleagues[60] found that 86% of respondents with either bipolar I or II disorder also met criteria for 3 or more other DSM-IV disorders. Obviously, it is difficult to study a representative sample with all comorbid conditions while controlling for all confounding factors. In fact, there is no consensus on what factors should be controlled for in independent variable analysis in patients with mood disorders and comorbid conditions. Thus it may be unwise to generalize the present results to other samples of individuals with bipolar disorder.

These findings must be considered in view of several methodological limitations. First, data for this report were derived from 4 different studies in a period of 10 years, in which suicide attempt was not the focus of study and in which the severity of suicide attempts was not measured. Although 4 studies were entered into the regression model, other potential confounding factors related to each study could not be totally eliminated. Second, not all anxiety disorders were assessed for all 4 studies. Therefore, associations of social phobia or posttraumatic stress disorder with the risk of suicide attempt were not able to be assessed. Third, recall bias could not be avoided although the requirement that a significant other be present during the baseline evaluation was intentionally employed to minimize the possible inaccuracy. Fourth, the severity of early life trauma was not assessed. More importantly, like other retrospective and cross-sectional studies, the relationship between attempted suicide and rapid-cycling course could not be established. In other words, rapid-cycling course could be an outcome or a predictor of attempted suicide.

CONCLUSION

In this cohort of patients with rapid-cycling bipolar disorder, more than 41% had at least 1 suicide attempt. Any comorbidity, history of drug abuse, psychosis during depression, early life physical abuse, female sex, and the bipolar I subtype were associated with increased risk and/or the number of previous suicide attempts. On the contrary, being of white race was associated with decreased risk and decreased number of previous suicide attempts.

Drug names: carbamazepine (Carbatrol, Equetro, and others), divalproex (Depakote and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), valproic acid (Stavzor, Depakene, and others).

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