

Bipolar Patients With Suicidal Behavior: Toward the Identification of a Clinical Subgroup

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Background: Suicide is the most severe and frequent complication of bipolar disorder, but little is known about the clinical characteristics of bipolar patients at risk of suicide. The purpose of this study was to identify those characteristics.

Method: We studied 307 prospectively recruited DSM-IV–diagnosed bipolar I or II patients from November 1994 through October 2001. Semi-structured diagnostic interviews (the Diagnostic Interview for Genetic Studies and the Family Interview for Genetic Studies) were used to determine the diagnosis of bipolar disorder and its lifetime description, lifetime comorbid Axis I disorder diagnoses, familial history of psychiatric disorders and demographic characteristics.

Results: One hundred twenty-nine bipolar patients (42%) had made at least 1 suicide attempt in their life. Lifetime history of suicidal behavior was associated with history of suicidal behavior in first-degree relatives but not with a familial history of mood disorder. Early age at onset of mood disorder, total number of previous depressive episodes, alcohol and tobacco use, social phobia, antidepressant-induced mania, and personal history of head injury were associated with suicidal behavior. No association was observed with gender or diagnosis of bipolar I or II disorder. Social phobias, tobacco use, and personal history of head injury were no longer associated with suicidal behavior in the multivariate analysis.

Conclusion: Bipolar patients with early age at bipolar disorder onset, high number of depressive episodes, personal history of antidepressant-induced mania, comorbid alcohol abuse, and suicidal behavior constitute a clinical subgroup at risk of suicidal behavior. This information, as well as familial history of suicide behavior, should improve suicide risk assessment in bipolar patients.

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Patients with bipolar disorder are at higher risk of suicidal behavior than those suffering from other psychiatric disorders.¹ Between 25% and 50% of bipolar patients attempt suicide at least once in their lifetime, and 8.6% to 18.9% of bipolar patients die due to completed suicide.² Although suicide is the major complication of this disorder, many bipolar patients never attempt suicide and there may thus be a difference between those who do and do not attempt suicide at least once. Although discrepant results have been published regarding risk factors and warning characteristics for suicidal behavior in bipolar patients, it has been suggested that familial and personal history of suicidal behavior,^{1,3–5} depressive and mixed states,^{6,7} and comorbid substance or alcohol abuse⁸ are associated with a high suicide risk in bipolar patients.

In contrast, conflicting results have been obtained concerning the relationships between suicidal behavior and gender, age, familial history of any mood disorder, number of previous major mood episodes, number of previous hospitalizations, duration of illness, presence of psychotic symptoms, and presence of comorbid conditions (such as anxiety disorders).^{4,5,8–12}

It is difficult to interpret such discrepancies due to several methodological limitations. First, most of the samples studied so far were composed of inpatients included before complete remission of mood episode, which might have influenced recall bias and therefore altered estimations of suicide attempt rate. Second, only a few studies have used multivariate analyses to investigate the interactions between these risk factors in large

samples. Third, discrepancies might have arisen due to clinical heterogeneity in the retained definition of suicidal attempt. The aim of our study was thus to explore further the clinical characteristics that might identify a clinical subgroup of euthymic bipolar patients at risk of suicide attempt.

MATERIALS AND METHOD

Sample

Inpatients and outpatients meeting DSM-IV criteria for bipolar I or II mood disorder ($N = 307$) were prospectively recruited in 2 university-affiliated hospitals (in Paris and Bordeaux, France) between 1994 and 2001. Data for this study were collected from November 1994 through October 2001. These patients are part of an ongoing genetic study. All subjects gave oral and written informed consent. After complete mood stabilization, as attested by Montgomery-Asberg Depression Rating Scale (MADRS)¹³ and Bech Rafaelson Mania Scale¹⁴ scores, the patients were interviewed by a trained psychiatrist with the Diagnostic Interview for Genetic Studies (DIGS).¹⁵ Information concerning demographic characteristics, history of medical disorders, diagnosis of bipolar disorder, and Axis I comorbid disorders was collected with the DIGS. The proband and at least 1 first-degree relative, when possible, were interviewed with the Family Interview for Genetic Studies (FIGS)¹⁶ to evaluate the psychiatric history of the proband's first-degree relatives. Age at onset of mood disorder was defined as the age at which the patient first met the DSM-IV¹⁷ criteria for either major depressive episode or manic or hypomanic episode. Suicide attempts were defined as self-destructive acts with some degree of intent to end one's life and severe enough to require hospitalization. Patients with behaviors that stopped short of an attempt as well as patients with self-destructive behavior with no intention of dying, self-mutilation to decrease anxiety, and suicide signals during social crises were considered to be nonsuicidal. Death intent was assessed in the "suicide" section of the DIGS. Only patients with a certain or serious intent were considered to be suicidal.

Statistical Methods

Patients with and without a history of suicidal behavior were compared in univariate analyses for all clinical and demographic characteristics. Categorical variables were compared by use of χ^2 tests or Fisher exact probability tests, as appropriate. Continuous variables were compared by use of independent-sample t tests. Logistic regression analysis was carried out using presence or absence of lifetime history of suicide attempt as the dependent variable and all clinical variables showing a p value below .1 in the univariate analysis as independent variables. A second regression analysis was performed in-

cluding only variables that showed a significant association with suicidal behavior in the first regression analysis. All statistical analyses were performed with StatView, version 5.0.1 (Cary, N.C.).

RESULTS

Three hundred seven bipolar patients (226 bipolar I, 81 bipolar II; 124 men, 183 women; mean \pm SD age = 44.2 ± 14.7 years) were included. Of those, 129 (42%) had a lifetime history of suicidal behavior (at least 1 suicide attempt). Mean age for the first suicide attempt was 32.25 ± 13.54 years and the mean number of suicide attempts was 2.25 ± 1.93 .

Univariate Analysis (Table 1)

Lifetime history of suicidal behavior was associated with the total number of major mood episodes ($t = -4$, $p < .0001$) and the total number of hospitalizations for a major mood episode ($t = -3.12$, $p = .002$). This was mainly due to a significantly higher number of major depressive episodes in patients with suicidal behavior ($t = -3.6$, $p = .0004$), even though the total number of manic episodes was also higher in suicide attempters ($t = -2.11$, $p = .04$). History of any substance misuse ($\chi^2 = 6.80$, $df = 1$, $p = .01$) was also associated with suicidal behavior. This association was mainly due to alcohol abuse, which was more frequent in bipolar patients with a history of suicidal behavior (26.4%) than in those without (12.4%) ($\chi^2 = 10$, $df = 1$, $p = .001$). Suicidal behavior was also associated with tobacco use (present or past) ($\chi^2 = 5.68$, $df = 1$, $p = .02$). In this analysis, lifetime history of suicide attempt was associated with early age at first mood episode ($t = 2.97$, $p = .003$), familial history of attempted or completed suicide ($\chi^2 = 5.51$, $df = 1$, $p = .02$), personal history of antidepressant-induced mania ($\chi^2 = 4.3$, $df = 1$, $p = .04$), social phobia ($\chi^2 = 4.32$, $df = 1$, $p = .04$), and personal history of head injury ($\chi^2 = 3.71$, $df = 1$, $p = .05$).

Multivariate Analysis

When controlling for the duration of the disease, the total number of mood episodes ($p = .022$, OR = 1.08, 95% CI = 1.01 to 1.16) and the early age at onset of the mood disorder ($p = .04$, OR = 0.97, 95% CI = 0.95 to 1) remained associated with lifetime history of suicide attempt in the multivariate analysis (Table 2). Logistic regression analysis showed that social phobia, personal history of head injury, and tobacco use were no longer associated with suicidal behavior, whereas absence of panic disorder with or without agoraphobia was associated with suicidal behavior ($p = .032$). All other associations remained significant (Table 3). Panic disorder with or without agoraphobia was no longer associated with suicidal behavior in the second regression analysis that only

Table 1. Comparison of Bipolar Patients With and Without a History of Suicide Attempt

Characteristic	Total N ^a	No History of Suicide Attempt	History of Suicide Attempt	p Value
Total no. of major mood episodes, mean ± SD (sample size)	265	5.1 ± 3.7 (156)	7.2 ± 4.8 (109)	<.0001
Total no. of major depressive episodes, mean ± SD (sample size)	287	3.3 ± 3.0 (164)	4.8 ± 4.1 (123)	.0004
Alcohol abuse, N/N (%)	306	22/178 (12.4)	34/128 (26.6)	.001
Total no. of hospitalizations for a major mood episode, mean ± SD (sample size)	286	3.7 ± 4.4 (166)	5.4 ± 5.2 (120)	.002
Age at onset of mood disorder, mean ± SD, y (sample size)	303	28.3 ± 12.1 (176)	24.4 ± 9.9 (127)	.003
Duration of illness, mean ± SD, y (sample size)	289	15.7 ± 12.8 (167)	19.7 ± 11.7 (122)	.007
Total duration of hospitalization, mean ± SD, wk (sample size)	138	13.6 ± 21.7 (88)	31.1 ± 53.0 (50)	.007
Age at first treatment for mood episode, mean ± SD, y (sample size)	306	30.8 ± 12.0 (177)	27.5 ± 9.7 (129)	.009
History of any substance misuse, N/N (%)	307	29/178 (16.3)	37/129 (28.7)	.01
Familial history of suicidal behavior, N/N (%)	307	31/178 (17.4)	37/129 (28.7)	.02
Tobacco use, N/N (%)	299	105/174 (60.3)	92/125 (73.6)	.02
Age at first hospitalization, mean ± SD, y (sample size)	298	35.4 ± 14.8 (172)	31.7 ± 12.3 (126)	.02
History of antidepressant-induced mania, N/N (%)	288	51/169 (30.2)	50/119 (42.0)	.04
Total no. of manic episodes, mean ± SD (sample size)	287	1.9 ± 2.2 (166)	2.6 ± 3.3 (121)	.04
Social phobia, N/N (%)	302	9/174 (5.2)	15/128 (11.7)	.04
History of head injury, N/N (%)	307	15/178 (8.4)	20/129 (15.5)	.05
Panic disorder with or without agoraphobia, N/N (%)	302	19/175 (10.9)	6/127 (4.7)	.06
Rapid cycling, N/N (%)	299	11/174 (6.3)	15/125 (12.0)	.09
Lithium response, N/N (%)	277	48/163 (29.4)	43/114 (37.7)	.15
Nature of the first mood episode, N/N (%)	302			.16
Manic with psychotic symptoms		22/177 (12.4)	8/125 (6.4)	...
Manic		15/177 (8.5)	15/125 (12.0)	...
Depressive with psychotic symptoms		13/177 (7.3)	9/125 (7.2)	...
Depressive		95/177 (53.7)	79/125 (63.2)	...
Hypomanic		30/177 (17.0)	14/125 (11.2)	...
Mixed		2/177 (1.1)	0/125	...
Generalized anxiety disorder, N/N (%)	180	2/101 (2.0)	5/79 (6.3)	.24
Alcohol dependence, N/N (%)	305	5/178 (2.8)	7/127 (5.5)	.25
Total no. of mixed episodes, mean ± SD (sample size)	263	0.2 ± 0.4 (152)	0.2 ± 0.5 (111)	.29
Carbamazepine response, N/N (%)	271	7/157 (4.5)	9/114 (7.9)	.3
Phobias, N/N (%)	300	7/172 (4.1)	2/128 (1.6)	.31
Gender, N/N (%)	307			.46
Male		75/178 (42.1)	49/129 (38.0)	...
Female		103/178 (57.9)	80/129 (62.0)	...
Obsessive-compulsive disorder, N/N (%)	301	4/173 (2.3)	5/128 (3.9)	.5
Familial history of mood disorder, N/N (%)	307	77/178 (43.3)	51/129 (39.5)	.51
Psychotic symptoms, N/N (%)	303	97/176 (55.1)	71/127 (55.9)	.9
Bipolar I, N/N (%)	307	131/178 (73.6)	95/129 (73.6)	.99
Bipolar II, N/N (%)	307	47/178 (26.4)	34/129 (26.4)	.99

^aPatients' lifetime interviews could not provide information for some characteristics; thus, statistical analyses were performed in the subsamples shown.

included variables that showed a significant association with suicidal behavior in the first regression analysis (Table 4). All remaining variables were significant in both logistic regression analyses.

DISCUSSION

In our cohort of 307 bipolar patients in remission, 42% had attempted suicide at least once in their life. This is in agreement with the ranges usually reported in bipolar patients (25%–50%).²

Our main result is that bipolar patients with early disease onset, numerous depressive episodes, history of antidepressant-induced mania, and a familial history of suicidal behavior are at high risk of suicide attempts.

There is an association between early onset of bipolar disorder and suicidal behavior. This may be because patients with early onset bipolar disorder have a longer dis-

ease duration on average (and thus a higher number of illness episodes). However, when taking into account the duration of the disease, we found an association between lifetime history of suicide attempt and (1) the number of mood episodes and (2) early age at onset of bipolar disorder.

The association between suicidal behavior and early age at onset of bipolar disorder has already been reported.¹⁸ We have previously reported the existence of 3 age-at-onset subgroups in bipolar disorder and showed that suicidal behavior is one of the characteristics of the early onset subgroup, possibly determined by specific genetic vulnerability factors.¹⁹

In our sample, lifetime history of suicidal behavior was associated with a history of suicidal behavior in first-degree relatives but not with familial history of mood disorder. This result is consistent with the hypothesis that the familial transmission of the risk for suicidal acts is

Table 2. Logistic Regression of the Association Between Suicidal Behavior, Total Number of Major Mood Episodes, Age at First Mood Episode, and Duration of Illness

Parameter	p Value	Odds Ratio (95% CI)
Total no. of major mood episodes	.022	1.08 (1.01 to 1.16)
Age at onset of mood disorder	.04	0.97 (0.95 to 1.00)
Duration of illness	.343	1.01 (0.99 to 1.04)

Table 3. Logistic Regression of the Association Between Lifetime History of Suicidal Behavior and Clinical Variables With $p < .1$ in the Univariate Analysis

Parameter	p Value	Odds Ratio (95% CI)
Age at onset of mood disorder	.022	0.97 (0.95 to 0.99)
History of antidepressant-induced mania	.037	1.84 (1.03 to 3.26)
Rapid cycling	.53	1.38 (0.50 to 3.75)
Familial history of suicidal behavior	.028	2.05 (1.08 to 3.9)
Tobacco use	.19	1.49 (0.82 to 2.70)
Alcohol abuse	.044	2.05 (1.02 to 4.11)
Panic disorder with or without agoraphobia	.032	0.29 (0.09 to 0.90)
Social phobia	.21	2.0 (0.67 to 5.80)
Personal history of head injury	.14	1.79 (0.82 to 3.90)

independent of the familial transmission of a mood disorder and other psychiatric disorders, as demonstrated by family,^{4,20-24} adoption,²⁵ twin,²⁶⁻²⁹ and molecular biological studies.³⁰⁻³² In particular, polymorphisms of the tryptophan hydroxylase gene and the serotonin transporter gene are associated with suicidal behavior regardless of the primary psychiatric diagnosis.^{33,34} Our results also suggest that familial history of suicidal behavior is a major warning sign that should systematically be assessed precisely. This recommendation has already been outlined in the American Psychiatric Association guidelines for the treatment of bipolar disorder.³⁵

Data on whether personal history of antidepressant-induced mania could be associated with lifetime occurrence of suicidal behavior are sparse. This observation suggests that suicidal behavior in bipolar patients is associated with a pattern of mood instability characterized by antidepressant-induced mania and a higher frequency of depressive relapses. This is also consistent with previous studies that showed a more severe disease course in suicidal patients.^{8,11}

Suicidal behavior was also associated with lifetime occurrence of alcohol abuse. However, this characteristic is not specific to bipolar patients, as it has often been reported in both bipolar and nonbipolar suicide attempters.^{5,6,36}

Several clinical characteristics (e.g., gender, bipolar I or II diagnosis, nature of first mood episode, total number of mixed episodes, presence of psychotic symptoms, rapid cycling, comorbid anxiety disorders, response to carbamazepine and lithium, and history of head injury)

Table 4. Logistic Regression of the Association Between Lifetime History of Suicidal Behavior and Variables With $p < .05$ in the First Multivariate Analysis

Parameter	p Value	Odds Ratio (95% CI)
Age at onset of mood disorder	.012	0.97 (0.95 to 0.99)
History of antidepressant-induced mania	.025	1.83 (1.08 to 3.10)
Familial history of suicidal behavior	.031	1.94 (1.06 to 3.55)
Alcohol abuse	.006	2.44 (1.28 to 4.65)
Panic disorder with or without agoraphobia	.097	0.42 (0.15 to 1.20)

were not associated with suicidal behavior in our sample of bipolar patients. The absence of a gender effect on suicidal behavior in our population may be the consequence of the inclusion criteria used here for suicide. We did not include completed suicides or parasuicides, the incidences of which are gender-dependent. Indeed, women are at a higher risk of parasuicide, whereas men complete suicide more frequently.^{37,38} As previously reported, we found no difference in mood disorder diagnosis (bipolar I/bipolar II) between the bipolar attempters and non-attempters,⁶ and there was no difference in presence of psychotic symptoms between the 2 groups.^{8,11,39} Literature about whether comorbid panic disorder is a risk factor or a protective factor for suicidal behavior in mood disorders remains very controversial.⁴⁰⁻⁴⁵ In our study, the first logistic regression suggested a protective role of comorbid panic disorder. This was not replicated in the second logistic regression analysis, suggesting either the absence of an association or a weak effect.

In our sample, we did not replicate the association previously reported between mixed episodes and suicidal behavior.^{7,38,46} This could be related to measurement bias, as retrospective diagnosis of mixed episodes is known to be difficult.

The interpretation of our data is limited by several factors. First, the retrospective assessment of suicidal behavior is strongly dependent on the patient's narrative abilities and therefore allows recall bias. We tried to minimize the impact of this bias by systematically assessing patients after complete remission of the mood episode. Second, the influence of censoring on our results remains unclear. Prospective long-term studies to assess patients during the acute stages of the mood disorder and after complete remission will provide more reliable results and overcome the problem of censoring.

In conclusion, in bipolar patients, a severe outcome (high number of depressive episodes, early age at onset, history of antidepressant-induced mania), comorbid alcohol abuse, and familial history of suicidal behavior may constitute major warning characteristics to identify subgroups at risk of suicidal behavior. In clinical practice, these characteristics should be systematically assessed.

Drug names: carbamazepine (Tegretol and others), lithium (Lithobid, Eskalith, and others).

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