Suicidal Risk Factors in Bipolar I and II Disorder Patients

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ABSTRACT

Background: Suicidal risks may be similar in bipolar I and II disorders, but predictive risk factors are not well established for each disorder type or across cultures.

Method: Accordingly, we compared selected demographic and clinical factors for long-term association with nonlethal suicidal acts or ideation in 290 *DSM-IV* bipolar I (n = 204) and II (n = 86) disorder patients followed for a mean of 9.3 years at the University of Barcelona, using preliminary bivariate comparisons followed by multivariate logistic regression modeling.

Results: Rates of suicidal ideation (41.5%) and acts (19.7%) were similarly prevalent with bipolar I and II disorders and somewhat more common among women. Factors significantly and independently associated with suicidal acts were determined by multivariate modeling and ranked in order of their strength of association: suicidal ideation, more mixed episodes, Axis II comorbidity, female sex, more antidepressant trials, rapid cycling, predominant lifetime depression, having been hospitalized, older onset, and longer delay of diagnosis. Suicidal ideation was associated with suicidal acts, more antidepressant trials, predominant depressions, more mixed-episodes/year, depressive first-lifetime episodes, electroconvulsive therapy use, delay of bipolar disorder diagnosis, unemployment, melancholic features, Axis II disorders, rapid cycling, and more depressions per year. Risk factors selectively associated with suicidal risk, overall, included more mixed-states per year and melancholic features, whereas hospitalization, unemployment, and predominantly depressive recurrences were more characteristic of diagnostic subtypes.

Conclusions: Suicidal risk-factors found to be independent of bipolar disorder diagnostic subtype included mixed-states, melancholic depressive features, and more antidepressant trials.

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Bipolar disorders are prevalent, often severe and disabling major psychiatric illnesses. Lifetime prevalence can be as high as 5%, if bipolar II disorder and cyclothymia are included.[1,2] Both bipolar I and II disorders can have devastating consequences on developmental, occupational, and social functioning, as well as high rates of mortality from all causes.[3–9] Major mood disorders, overall, are currently the third-leading cause of disability on a worldwide basis.[10] A substantial component of the disease-burden in bipolar disorder is related to suicide.[11] Suicide rates among patients suffering from bipolar disorder can be more than 20 times higher than the general population rate of approximately 0.015%/y.[12] This risk is greater than other psychiatric, substance use, and general medical disorders, including major depressive disorder across its broad range of severities.[12,13] Suicide accounts for 15%–20% of deaths among bipolar disorder patients,[1,12] with particularly high risk early in the course of the illness.[12,14] Several risk factors have been identified that are associated with suicidal risk in bipolar disorder patients, including current depression or mixed states, previous severe depression or suicide attempts, Caucasian ethnicity, being unmarried, current feelings of hopelessness, hostility, active abuse of alcohol or illicit drugs, limited access to support or clinical services, early sexual abuse, Axis II comorbidity, life stressors, and some aspects of medical comorbidity, including obesity and metabolic syndrome.[15–18] However, relationships of risk factors to suicidal ideation or behavior require further clarification, specifically in comparisons of bipolar I and II disorder patients.[16,19–21]

METHOD

We compared demographic and clinical factors for association with nonlethal suicidal acts or reported suicidal ideation in patients at the University Hospital of Barcelona, Spain, with initial bivariate comparisons followed by multivariate logistic regression modeling.

Study Design and Participants

This prospective, naturalistic, cohort study involved 290 adult patients evaluated, treated clinically, and followed at the Bipolar Disorder Program of the Hospital Clinic of the University of Barcelona. All participants (41.4% of eligible bipolar disorder adult patients) provided written, informed consent to participate and for aggregate and anonymous reporting of their clinical findings, following review and approval by the Hospital ethical review committee.

Inclusion required meeting *DSM-IV* diagnostic criteria for bipolar I (n = 204) or II (n = 86) disorders, based on clinical assessments of patients and at least 1 first-degree relative and on review of medical records—all supported by Structured Clinical Interviews for *DSM-IV* Axes I and II (SCID).[22] Current and previous treatments were selected clinically, independent of the study protocol, and could include lithium carbonate, anticonvulsants, antidepressants, antipsychotics, or electroconvulsive therapy (ECT). Patients with major medical comorbidities sufficiently severe as to be associated with functional disability were excluded.

In addition to standard clinical and demographic characteristics of patients, predominant polarity was rated as ≥ 67% of all mood episodes being either depressive or manialike (mania, hypomania, mixed states),

Clinical Points

- Suicidal risk was remarkably similar in types I and II bipolar disorder patients.
- Manic-depressive mixed-state recurrences were especially strongly associated with suicidal risk.
- Suicidal risk also was associated with melancholic depression and more trials of antidepressants.

based on *DSM-IV* diagnostic criteria.[23] Age at onset is the approximate age at first clinical manifestations in illnesses later diagnosed as bipolar disorder. Outcomes are self-reported lifetime experiences with suicidal ideation or any nonfatal, self-injurious acts and as assessed on each clinic visit as a specific component of each clinical interview as well as by tracking the suicide item (#3) of the 17-item Hamilton Depression Rating Scale[24] in its validated Spanish language version.[25] All patients also were followed weekly for ≥ 12 weeks through and following an acute index episode of major depression, during which their suicidal behaviors were assessed specifically for potential lethality.

Data Analyses

Analyses involved preliminary bivariate comparisons of rates of factors associated with patients reporting suicidal ideation or acts or not. Continuous factors were evaluated by analysis of variance methods (F) and categorical factors by contingency tables (χ^2), with Bonferroni-adjusted probability values (P) indicated. Factors that appeared to be associated with suicidal acts or thoughts in these preliminary analyses (bivariate $P \leq .10$) were then subjected to multivariate, logistic regression modeling to provide odds ratios (ORs) and their 95% confidence intervals (CIs), with stepwise inclusion of factors in descending order of their strength of preliminary associations. Data are shown as mean ± SD unless stated otherwise.

RESULTS

General Characteristics

The 290 bipolar disorder subjects included 204 bipolar I and 86 bipolar II disorder patients, ill for a total of 18.7 ± 10.6 years, and followed at the study site for 9.29 ± 5.40 years (median = 9.00; range, 1–21 years; bipolar I disorder, 9.46 ± 5.48 years; bipolar II disorder, 8.87 ± 5.20 years), typically at a rate of 4–12 visits/y, with various clinically determined treatments over time. Current age was 47.9 ± 14.1 years, and it did not differ significantly by sex or diagnosis. Suicidal ideation was detected in 41.5% (n=120) of all subjects; and suicidal acts, 19.7% (n = 57). Lifetime rates of suicidal ideation were significantly greater among bipolar II than bipolar I disorder patients (53.5% vs 36.7%; $\chi^2 = 5.83$, $P = .016$), but rates of suicidal acts were very similar (20.1% and 19.7%, respectively). In women (n = 149) versus men (n = 141), risks of both suicidal ideation (46.8% vs 36.2%) and behaviors (29.8% vs 9.48%) were lower among men (completed suicides were not considered). Of suicidal acts or attempts, 54.2% were potentially lethal but for timely interventions. This proportion did not differ significantly by sex and was nonsignificantly more likely among bipolar II than bipolar I disorder patients (64.3% vs 50.0%). The number of suicide attempts/person-year was 0.021 ± 0.054 (or about 2 per 100 person-years). This rate did not differ significantly by diagnosis, but it was greater among women than men (0.032 ± 0.067 vs 0.009 ± 0.031; $F = 11.6$, $P = .0008$).

Risk Factors for Suicidal Acts and Ideation

Factors preliminarily associated with nonlethal, lifetime suicidal acts included suicidal ideation; more mixed manic-depressive episodes/y; any Axis II disorder; female sex; more antidepressant trials; previous rapid cycling (≥ 4 recurrences in a year); having ≥ 2:1 more depressions than mania-like recurrences; history of mood disorders among first-degree relatives; ever being psychiatrically hospitalized; being unemployed; having received ECT, any postpartum psychiatric illness among women, longer delay from illness onset to diagnosis of bipolar disorder, depressive first-lifetime episode; and having shown melancholic features of depression (Table 1). The last 6 factors did not meet the Bonferroni-adjusted critical P value of ≤ .003. Additional factors not associated with suicidal acts included marital status; living independently; education; diagnostic subtype (bipolar I or II disorder); any comorbid Axis I disorder; any type of substance abuse; age at onset; current age; years ill; number of episodes, manias, hypomanias, or depressions per year; ever showing psychotic features; notable seasonal mood shifts; "atypical" depressive features; mean duration of antidepressant trials; being nonresponsive to antidepressant treatment at any time; treatment with a mood stabilizer in the past; prior switching from depression to mania/hypomania within 8 weeks of antidepressant treatment; and having been considered treatment noncompliant.

Factors associated preliminarily with suicidal ideation included suicidal acts, more antidepressant trials, predominantly depressive recurrences, more mixed episodes/y, depressive first episode, ever given ECT, longer latency from onset to bipolar disorder diagnosis, being unemployed, having had melancholic features of depression, any comorbid Axis II disorder, previous rapid cycling, more depressions/y, comorbid anxiety disorder, bipolar I disorder diagnosis, total years of illness, and more episodes/y (Table 1). The last 4 factors did not meet the Bonferroni-adjusted critical P value of ≤ .003). Factors not associated with suicidal ideation included family history, sex, age at onset, current age, years ill, marital status, living independently, education, any psychotic features, having been hospitalized, seasonal mood shifts, any postpartum illness among women, any treatment nonadherence, alcohol or drug abuse, average duration of antidepressant trials, past treatment with a mood stabilizer, switched mood with an antidepressant, having been considered antidepressant-nonresponsive, and manias or hypomanias/y.

Table 1. Factors Associated With Suicidal Behavior Among 290 Bipolar Disorder Patients[a]

Factor	Suicidal	Nonsuicidal	Relative Risk	F or χ^2	P Value
Suicidal acts (lifetime)					
History of suicidal ideation, %	100	0.00	> 100	84.0	< .0001
No. of mixed episodes/y, mean ± SD	0.078 ± 0.132	0.017 ± 0.042	4.59	28.5	< .0001
Any Axis II disorder, %	45.8	16.7	2.74	18.7	< .0001
Sex, %				15.5	< .0001
Female	77.1	45.3	1.70		
Male	22.9	54.7	0.42		
No. of antidepressant trials, mean ± SD	4.42 ± 2.78	2.76 ± 2.59	1.60	15.3	.0001
Any rapid-cycling, %	37.5	13.5	2.78	14.7	< .0001
Predominant depressions, %[b]	81.5	48.2	1.69	9.73	.002
Familial mood disorder, %	51.8	18.5	2.80	9.73	.002
Prior psychiatric hospitalization, %	91.7	70.3	1.30	9.24	.002
Unemployed, %	72.9	51.0	1.44	7.44	.006
Given ECT, %	27.1	12.0	2.26	6.87	.009
Postpartum illness, %	18.8	9.90	1.90	7.64	.02
Latency to diagnosis, mean ± SD, y	9.19 ± 10.0	6.38 ± 8.11	1.44	4.17	.04
Depressive onset, %	72.9	56.8	1.28	4.17	.04
Melancholic at any time, %	47.9	32.3	1.48	4.10	.04
Suicidal ideation (lifetime)					
History of suicidal acts, %	48.0	0.00	≥ 48	84.0	< .0001
No. of antidepressant trials, mean ± SD	4.09 ± 2.87	2.38 ± 2.34	1.72	25.8	< .0001
Predominant depressions, %[b]	75.9	41.4	1.83	16.0	< .0001
No. of mixed episodes/y, mean ± SD	0.050 ± 0.103	0.014 ± 0.035	3.57	14.7	.0002
Depressive onset, %	74.0	50.0	1.48	14.0	.0002
Given ECT, %	25.0	7.86	3.18	13.4	.0002
Latency to diagnosis, mean ± SD, y	9.25 ± 10.3	5.29 ± 6.63	1.75	13.0	.0004
Unemployed, %	69.0	45.7	1.51	12.8	.0003
Melancholic at any time, %	48.0	26.4	1.82	11.9	.0006
Comorbid Axis II disorder, %	33.0	15.0	2.20	10.8	.001
Rapid cycling, %	28.0	11.4	2.46	10.7	.001
No. of depressions/y, mean ± SD	0.507 ± 0.390	0.354 ± 0.370	1.43	9.52	.002
Comorbid anxiety disorder, %	50.0	32.9	1.52	7.14	.007
Diagnosis, %				5.83	.02
Bipolar I	36.7	63.3	0.58		
Bipolar II	53.5	46.5	1.15		
Total years of illness, mean ± SD	21.4 ± 11.2	18.4 ± 10.2	1.16	4.82	.03
No. of episodes/y, mean ± SD	0.917 ± 0.698	0.740 ± 0.594	1.24	4.42	.04

[a]Factors are ranked by statistical significance; Bonferroni-adjusted $P \leq .003$ (0.05/15).
[b]≥ 2:1 more depressions than manias, hypomanias, or mixed states.
Abbreviation: ECT = electroconvulsive therapy.

Table 2. Multivariate Logistic Regression Models of Factors Associated With Suicidal Risks[a]

Factor	Odds Ratio (95% CI)	χ^2	P Value
Suicidal acts			
More mixed episodes/y	26.1 (10.1–41.9)	13.0	.0003
Female sex	11.5 (2.80–47.6)	11.5	.0007
Predominantly depressed	5.46 (1.30–23.0)	5.36	.02
Latency to bipolar diagnosis	1.06 (1.00–1.13)	3.70	.05
Suicidal ideation			
Predominantly depressed	4.74 (1.94–11.6)	11.6	.0007
More mixed episodes/y	20.1 (6.82–33.4)	11.1	.0009
Melancholic at any time	2.82 (1.24–6.39)	6.16	.01

[a]Based on analysis of 290 patients with bipolar I (n = 204) or II (n = 86) disorder.

Based on multivariate modeling of factors differing at $P \leq .003$ (Bonferroni-adjusted for multiple comparisons) in Table 1, those remaining significantly and independently associated with suicidal acts (omitting suicidal ideation as circular) were ranked in order of their strength of association: more mixed-episodes/y, female sex, predominantly depressive recurrences, and years from onset to diagnosis of bipolar disorder (Table 2). Factors associated with suicidal ideation were ranked in order of their strength of association: recurrences predominantly depressive, more mixed episodes/y, and melancholic features identified previously (Table 2).

Suicidal Risk Factors and Diagnosis

Factors identified individually as possibly associated with suicidal ideation or acts (15 factors, omitting suicidal ideation or acts as redundant; Table 1) were considered further for independent association with overall suicidal risk as contrasted to potential differences between bipolar I and II disorder patients (Table 3). This was done by multivariate modeling, with suicidal risk and diagnostic type as outcome variables in the same model. The results indicate that suicidal risk, but not diagnosis, was independently and significantly associated with a higher rate of mixed manic-depressive states/y, lifetime presence of melancholic features, and more antidepressant trials; in addition, bipolar II disorder compared to bipolar I disorder was nonsignificantly associated with more suicidal risk (including ideation as well as acts; $\chi^2 = 3.47$, $P = .06$). Conversely, bipolar I disorder was more associated with more psychiatric hospitalizations/y, and more unemployment, whereas bipolar II disorder was more associated with predominantly (≥ 2:1) depressive polarity of lifetime recurrences, all as expected.

DISCUSSION

Notable findings include very similar risks and rates of suicidal acts among bipolar I and II disorder patients, slightly more suicidal ideation and somewhat higher proportion of potentially lethal acts among bipolar II disorder patients. In accord with previous findings,[3,19–21,26] the present observations support the impression that suicidal risks are not lower among bipolar II than in bipolar I patients and that bipolar II disorder is not a milder or attenuated variant of bipolar I disorder.[26–31] Nevertheless, longitudinal comparisons of morbidity characteristics of bipolar I and II disorders remain remarkably sparse, and risk factors selective for bipolar I and II disorder patients required clarification.

Factors associated with suicidal acts and ideation, overall, appeared largely to represent more prominent and severe bipolar depression (Tables 1 and 2), including more mixed states, melancholic features, and antidepressant trials,

Table 3. Multivariate Logistic Regression Modeling of Factors Associated With Suicidal Risk and Bipolar Diagnostic Subtypes[a]

	Suicidal Risk		Bipolar I > II	
Factor	Odds Ratio (95% CI)	χ^2 (*P* value)	Odds Ratio (95% CI)	χ^2 (*P* value)
Mixed-states/y	15.8 (12.7 to 28.5)	7.44 (.006)	0.00 (0.00 to 1,000)	0.01 (.98)
Melancholic at any time	3.23 (1.37 to 7.59)	7.21 (.007)	2.07 (0.70 to 6.09)	1.73 (.19)
Antidepressant trials	1.29 (1.04 to 1.61)	5.22 (.02)	1.11 (0.86 to 1.44)	0.69 (.41)
Hospitalizations/y	2.71 (0.69 to 10.6)	2.04 (.15)	159 (6.38 to 1,000)	5.98 (.01)
Unemployed	1.70 (0.67 to 4.30)	1.25 (.26)	3.42 (1.15 to 10.2)	4.85 (.03)
Predominant depression	1.05 (1.91 to 6.27)	1.14 (.29)	−14.4 (−2.91 to −71.4)	10.7 (.001)

[a]Regression modeling involved risk of suicidal ideation or acts as well as diagnosis as separate outcome measures, considering 15 factors that were tentatively associated with suicidal risk in Table 1 (with Bonferroni-adjusted $P \leq .003$). Factors are ranked by significance of association with suicidal risk.

independent of bipolar I versus II disorder diagnoses (Table 3). Depression as the predominant polarity (by an excess of ≥2:1) of illness episodes was preliminarily associated with suicidal ideation and attempts (Table 1), as has been noted previously,[23,32–35] but was more characteristic of the natural history of bipolar II disorder when diagnosis was also considered (Table 3). Other risk factors identified and sustained in multivariate regression modeling, with respect to suicide attempts (Table 2), in addition to more mixed episodes/y and predominant depression, included greater risk among women than men, and longer delay between illness onset and the diagnosis of bipolar disorder, in accord with previous reports.[3,17,19] Longer delay of the diagnosis of bipolar disorder probably reflects an excess of initial and later depressive rather than manic or hypomanic illness.[1] Suicidal ideation also was associated with predominant depression and more mixed states, as well as with melancholic features of depression (Table 2).

The prominence of mixed-dysphoric states as well as depressions as risk factors for suicidal ideation and suicide attempts in bipolar disorder patients is increasingly recognized.[36,37] This association calls for close consideration of mixed features in the assessment of depressed bipolar disorder patients, including anger or anguish and agitation with dysphoria, to be differentiated from both depression and mania.[1,38] The present findings also underscore the need for effective and well-tolerated treatment options for depressive and mixed states in bipolar disorder patients and for explicit assessments of the ability of treatments to reduce suicidal risk.[38] Currently, treatments for bipolar depression and optimal management of mixed states remain far from satisfactory.[35–37] For bipolar disorder, substantial but incomplete evidence suggests that long-term treatment with lithium salts is associated with reduced rates of suicides and attempts,[39,40] possibly more so than anticonvulsants with putative mood-stabilizing properties.[41] To date, only clozapine has received regulatory approval for reducing some aspects of suicidal behaviors, and only among patients diagnosed with schizophrenia.[42,43]

The observed differences between bipolar I and II disorder patients accord with clinical expectations arising from the epidemiology of the bipolar disorder subtypes.[1] These include more hospitalizations/y, being unemployed, and having less prominent depression than bipolar II disorder patients (Table 3). However, none of these characteristics was independently associated with suicidal risk (Table 3).

This study has notable limitations. They include largely retrospective assessments of clinical history, including approximate onset-age and previous occurrences of suicidal behavior and, particularly, suicidal ideation. It also may be that the relatively low risks of suicidal ideation and attempts observed among men (Table 1) represent underreporting. It is also not clear whether these findings in a specialized academic clinic in Barcelona would generalize to other settings.

In conclusion, this study in a Spanish clinical sample of 290 consecutive patients diagnosed with *DSM-IV* bipolar I or II disorders underscores the growing impression that bipolar II disorder patients have high levels of morbidity, disability, and mortality. The study identified or verified factors associated with risk of suicidal behaviors or ideation. They generally accord with more severe illness or more prominent mixed and depressive morbidity (Table 2). In addition, factors selectively associated with suicidal risk and not diagnosis were the presence of mixed states, melancholic features of depression, and more antidepressant treatment trials, whereas psychiatric hospitalizations, lack of employment, and predominant depression, while tentatively associated with suicidal risk, were more characteristic of the type of bipolar disorder (Table 3). More clinical and pharmacologic studies are needed to assess suicidal risk and its prediction and prevention in bipolar disorder patients, especially of bipolar II disorder, as well as greater efforts to develop potentially effective and safe means of treating depressive and mixed states, as well as to limit suicidal risk and other adverse effects of such states.

Drug names: clozapine (FazaClo, Clozaril, and others), lithium (Lithobid and others).

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