On page 1517, the spelling of Dr. Pacchiarotti's name has been corrected in the byline and in the footnotes to the article.

Relevance of Family History of Suicide in the Long-Term Outcome of Bipolar Disorders

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Objective: This study examined the association between family history of completed suicide and suicidal behavior and other clinical variables in subjects with bipolar disorder.

Method: 374 outpatients aged from 19 to 88 years (mean ± SD age = 41.9 ± 4.1 years) (54.3% female) meeting DSM-IV criteria for bipolar disorder type I or II or schizoaffective disorder, bipolar subtype, were included in the study. Forty-eight subjects with a family history of completed suicide were compared to 326 subjects without a family history of completed suicide regarding several clinical and demographic variables. The study was conducted from 2001 to 2004.

Results: There were no statistically significant demographic differences between bipolar disorder subjects with and without a family history of suicide. Bipolar disorder subjects with a family history of suicide showed higher rates of cluster C personality disorders than subjects without a family history of suicide (14.9% vs. 2.5%, OR = 6.72, 95% CI = 2.31 to 19.51, p < .001). Subjects with a family history of suicide also demonstrated a significantly greater lifetime prevalence of suicide attempts (52.2% vs. 25.5%, OR = 3.19, 95% CI = 1.7 to 6.0, p < .001). Results remained significant after controlling for all possible interactions.

Conclusion: Family history of completed suicide is a significant risk factor associated with suicidal attempts in patients with bipolar disorder. These findings underscore the importance of identifying patients with a family history of suicide in order to provide prompt treatment and careful follow-up.

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Suicidal ideation and attempts are strongly associated with severe psychiatric disorders, particularly bipolar disorder.[1–3] In fact, approximately 30% of bipolar subjects attempt suicide in their lifetime.[4] Risk factors related to suicidal behavior in bipolar disorder include early age at onset, comorbid alcohol abuse, recurrent depressive episodes, previous suicidal attempts, mixed episodes, and poor adherence to treatment,[5–8] among others.

In addition, previous studies have shown that family history of suicidal behaviors is a strong risk factor for suicidality in bipolar subjects.[6,7] These studies selected bipolar patients who did and did not attempt suicide and then evaluated their family history for suicidality. To our knowledge, 2 studies[9,10] have evaluated the risk of suicidality in bipolar subjects using the opposite methodology, namely, stratifying the sample by family history of suicide. Employing chart reviews, these studies found that suicidal behavior was more frequent among bipolar pa-

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tients with a family history of suicide. Others have shown that suicidality appears to run in families independently of the history of psychiatric disorders.[11]

The goal of our study was to replicate and extend the results of previous findings by comparing the rates of suicidality and other demographic and clinical variables in bipolar subjects with and without a family history of completed suicide and using standardized psychiatric evaluations instead of chart reviews.

METHOD

All subjects included in this study were systematically and prospectively evaluated monthly during a period of up to 4 years through the Bipolar Disorders Program of the Hospital Clinic and University of Barcelona (Spain).[12,13] After approval by the Ethical and Research Committee of the University of Barcelona, informed consent was obtained, and demographic and clinical data were ascertained using the instruments described below. The study was conducted from 2001 to 2004.

Three hundred seventy-four outpatients aged from 19 to 88 years (mean ± SD age = 41.9 ± 4.1 years) fulfilling DSM-IV criteria for bipolar disorder type I or II or schizoaffective disorder, bipolar subtype, were included in this study. At intake, subjects were assessed by a psychiatrist using the Structured Clinical Interview for DSM-IV Axis I and Axis II Disorders.[14] The following clinical variables were examined: age at bipolar disorder onset; number and polarity of previous mood episodes; lifetime history of psychosis, suicidal behaviors, and substance abuse; current comorbid disorders; pharmacologic treatment; number of hospitalizations; and history of completed suicide in first- and second-degree relatives.

Lifetime suicidal ideation was considered to be present only in patients who endorsed ever having active thoughts of killing themselves. Suicide attempts were considered medically serious if hospitalization was necessary for medical or surgical reasons.[15] Suicide attempts were classified using the criteria of Arora and Meltzer,[16] in accordance with the violence of the attempt. Voluntary self-poisoning with drugs or other substances and single superficial skin cuts were considered nonviolent methods. Other methods such as jumping from a height, throwing oneself in front of a train, hanging, shooting, piercing, or a combination of these methods were considered violent.

For the purpose of analyses, the sample was stratified into 2 groups according to the presence of family history of completed suicide. Forty-eight subjects (48/374, 12.8%) had a family history of completed suicide (FHS+), and 326 (326/374, 87.2%) did not (FHS–). The groups were compared using univariate logistic regression analyses for the above noted demographic and clinical variables. Variables showing a p value below .25 were included in a multiple regression analysis. All possible interactions were tested before a final model was determined. Statistics were 2-tailed, and significance was set at $p \leq .05$. Odds ratios (ORs) and confidence intervals (CIs) were calculated to determine the effect of any statistically significant association.

RESULTS

Results of the univariate analysis are shown in Tables 1 and 2. There were no significant demographic differences between FHS+ and FHS– subjects. Regarding clinical characteristics, there were no significant differences between the groups in age at onset; lifetime history of psychotic symptoms or psychotic depression; lifetime substance use; number of manic, hypomanic, and depressive episodes; number of hospitalizations; bipolar subtype (bipolar I, bipolar II, or schizoaffective disorder); or pharmacologic treatment.

There were no statistically significant differences in the rates of comorbid Axis I disorders, but there were statistical differences in the rates of personality disorders. Specifically, FHS+ subjects showed higher rates of cluster C personality disorders than FHS– subjects (14.9% vs. 2.5%, OR = 6.72, 95% CI = 2.31 to 19.51, $p < .001$). There were no significant differences in the rates of cluster A or B personality disorders.

Compared with FHS– subjects, FHS+ subjects were significantly more likely to report a lifetime history of suicide attempts (52.2% vs. 25.5%, OR = 3.19, 95% CI = 1.7 to 6.0, $p < .001$) and reported a significantly greater mean number of previous attempts (0.9 ± 1.3 vs. 0.5 ± 1.1, OR = 1.28, 95% CI = 1.02 to 1.6, $p = .03$). Moreover, there was a trend for more suicidal ideation in subjects with a family history of completed suicide (75.0% vs. 62.4%, OR = 1.81, 95% CI = 0.88 to 3.72, $p = .11$). There were no differences between groups in the methods or medical severity of suicide attempts.

Number of previous attempts was no longer associated with family history of suicide in logistic regression analyses (Table 3). After controlling for all possible interactions, lifetime history of attempted suicide ($p = .002$, OR = 2.80, 95% CI = 1.44 to 5.44) and comorbid cluster C personality disorders ($p = .002$, OR = 5.8, 95% CI = 1.84 to 18.25) remained significantly associated with family history of suicide.

DISCUSSION

Bipolar disorder subjects with a family history of completed suicide have a significantly greater lifetime prevalence of suicide attempts as compared to bipolar disorder subjects without a family history of completed suicide. No other demographic or clinical variables besides cluster C comorbidity differentiated the 2 groups. These findings are convergent with previous findings. For example,

Table 1. Comparison of Bipolar Disorder Subjects With Versus Without a Family History of Suicide

Variable	Family History of Suicide	No Family History of Suicide	p Value
Age, mean ± SD y (N)	44.3 ± 14.1 (48)	41.5 ± 14.1 (325)	.19
Age at onset, mean ± SD y (N)	27.6 ± 12.4 (44)	26.8 ± 11.3 (318)	.67
Gender, female, N/N (%)	30/48 (62.5)	173/326 (53.1)	.22
No. of episodes, mean ± SD (N)			
Manic episodes	2.7 ± 5.6 (29)	2.4 ± 3.8 (224)	.69
Hypomanic episodes	3.5 ± 5.3 (28)	4.2 ± 8.6 (223)	.66
Depressive episodes	7.1 ± 7.6 (29)	6.4 ± 8.2 (227)	.64
Mixed episodes	0.5 ± 1.3 (29)	0.5 ± 1.3 (225)	.88
Any Axis I comorbidity (current), N/N (%)			
Substance abuse disorder	4/41 (9.8)	40/295 (13.6)	.47
Anxiety disorder	3/41 (7.3)	14/295 (4.7)	.58
Eating disorders	1/41 (2.4)	8/295 (2.7)	.87
Axis II comorbidity (current), N/N (%)			
Cluster A	2/47 (4.3)	13/315 (4.1)	.96
Cluster B	3/47 (6.4)	32/315 (10.2)	.41
Cluster C	7/47 (14.9)	8/315 (2.5)	< .001
Personality disorder NOS	2/47 (4.3)	11/315 (3.5)	.68
Lifetime substance abuse, N/N (%)	20/48 (41.7)	151/325 (46.5)	.53
Psychotic depression (lifetime history), N/N (%)	8/24 (33.3)	52/189 (27.5)	.55
Psychotic symptoms (lifetime history), N/N (%)	25/46 (54.3)	196/320 (61.3)	.37
Diagnosis, N (%)			.77
Bipolar disorder type I	25/48 (52.1)	184/321 (57.3)	
Bipolar disorder type II	18/48 (37.5)	104/321 (32.4)	
Schizoaffective disorder	5/48 (10.4)	33/321 (10.3)	
Current medication, N/N (%)			
Mood stabilizer	37/46 (80.4)	242/316 (76.6)	.56
Antidepressant	18/44 (40.9)	118/311 (37.9)	.70
Antipsychotic	21/43 (48.8)	141/302 (46.7)	.92
No. of hospitalizations, mean ± SD (N)	1.9 ± 3.3 (31)	1.5 ± 2.1 (230)	.38
Suicidal ideation (lifetime history), N/N (%)	33/44 (75.0)	189/303 (62.4)	.11
Attempted suicide (lifetime history), N/N (%)	24/46 (52.2)	81/318 (25.5)	< .001
No. of previous suicidal attempts, mean ± SD (N)	0.9 ± 1.3 (40)	0.5 ± 1.1 (289)	.03
Method, N/N (%)			.80
Violent	4/18 (22.2)	18/72 (25.0)	
Nonviolent	14/18 (77.8)	54/72 (75.0)	
Medical seriousness, N/N (%)			.39
Serious	7/16 (43.8)	23/71 (32.4)	
Nonserious	9/16 (56.3)	48/71 (67.6)	

Abbreviation: NOS = not otherwise specified.

Table 2. Odds Ratios of the Associations Between Family History of Suicide and Clinical Variables With p < .25 in the Univariate Analysis

Variable	p Value	Odds Ratio (95% CI)
Age	.19	1.01 (0.99 to 1.03)
Gender	.22	0.68 (0.36 to 1.27)
Cluster C personality disorder	< .001	6.72 (2.31 to 19.51)
Suicidal ideation	.11	1.81 (0.88 to 3.72)
Attempted suicide (lifetime history)	< .001	3.19 (1.70 to 6.00)
No. of previous suicidal attempts	.03	1.28 (1.02 to 1.60)

Table 3. Logistic Regression of the Associations Between Family History of Suicide and Attempted Suicide and Cluster C Personality Disorder

Variable	p Value	Odds Ratio (95% CI)
Cluster C personality disorder	.002	5.8 (1.84 to 18.25)
Attempted suicide (lifetime history)	.002	2.80 (1.44 to 5.44)

Mitterauer et al.[9] found that the rate of suicide attempts in subjects with a family history of suicide was 3-fold higher than in subjects without a family history of suicide. Additionally, Roy[10] also reported higher rates of suicide attempts in inpatients with several psychiatric disorders with a family history of completed suicide when compared to inpatients without a family history of suicide (48.6% vs. 21.8%, OR = 3.3). It appears that one of the most important risk factors associated with a suicidal attempt is family history of suicide.

Other epidemiologic and clinical studies have also underscored the important association between family history of suicidality and increased risk of suicidal behavior among probands.[17–19] For example, Goodwin et al.,[18] in a community sample, found that parental suicide attempt was associated with increased likelihood of suicide attempts among their offspring. Thus, suicidal behavior seems to run in families independent of their psychopathology, and this familiality may be accounted for by genetic factors.[11] An alternative explanation in addition to inherited genetic factors is that the experience of suicide in the family may also be learned or become an acceptable method to cope with severe adversity or symptoms. How-

ever, adoption studies[11] show a high correlation between adoptee suicide rates and suicide rates in biological relatives with whom adoptees have had no contact, and a lack of correlation between suicide in the adoptee and adoptee relatives.

The present findings also converge with those of Benazzi,[3] who found no association between suicidal ideation and family history of suicide behavior in subjects with bipolar disorder type II. Brent et al.[17] found a higher rate of attempted and completed suicide in the relatives of completed suicide victims as well as a higher rate of suicidal ideation. However, after controlling for family psychopathology, differences in suicidal ideation were no longer significant. Goodwin et al.[18] also reported that after adjusting for parental psychopathology, only parental suicidal attempts were associated with an increased likelihood of suicidal attempts in offspring. Lieb at al.[20] reported that suicidal behavior—but not suicidal ideation—was transmitted from mothers to their offspring. In a recent review, Brent and Mann[11] suggested that the familial transmission of suicidal ideation is related to the transmission of psychiatric disorders, but suicidal behavior cannot be explained only by the transmission of the psychiatric disorder.

Tsai et al.[7] found that mood-congruent psychotic symptoms decreased the risk of suicide. Although the present study did not examine for the mood congruence of psychotic symptoms, there were no differences in lifetime psychotic symptoms between subjects with a family history of suicide (54.3%) and those without a family history of suicide (61.3%). Rates of lifetime psychotic symptoms were similar to those presented in the study by Tsai et al. (63.4% for the total sample). There were no significant between-group differences in the psychopharmacologic treatments (mood stabilizers, antidepressants, and antipsychotics), suggesting that the differences in suicide attempts were not related to pharmacologic treatment. Contrary to the findings of Rihmer and Kiss,[21] there was not a greater prevalence of bipolar disorder type II among relatives of suicide completers.

Regarding comorbidity, there were no differences in Axis I current comorbidity between the groups. The rates of Axis I current comorbidity were similar to those in other studies that have shown lower rates of current Axis I comorbidity than lifetime Axis I comorbidity.[13,22] Contrary to previous findings, there were no differences in rates of lifetime substance use between groups. Potash et al.[23] found that alcoholism in bipolar disorder subjects was associated with significantly increased rates of attempted suicide among probands as well as among family members. A possible linkage between substance abuse and family history of suicide could not be replicated in this study.

Rates of Axis II personality disorder comorbidity were similar to those reported by George et al.[24] Interestingly, subjects with a family history of suicide were significantly more likely to have cluster C personality disorder comorbidity, even after adjusting for several possible confounders. Studies have suggested that comorbidity with personality disorders has a major impact on suicidal behavior in bipolar I and II patients.[13,25,26] In one preliminary study, Roy[27] compared personality characteristics using the Eysenck Personality Questionnaire (EPQ) in psychiatric patients with a family history of suicide and matched patients without a family history of suicide. Our present findings converge with those of Roy, showing higher neuroticism scores in patients with a family history of suicide, whereas no differences were reported for EPQ scores for psychoticism or extraversion. Results of a longitudinal study[28] of 1265 individuals followed for 21 years showed that neuroticism at age 14 was associated with later suicidal behavior. The finding of higher rates of cluster C personality among subjects with a family history of suicide raises the question about a possible linkage of transmission of suicidal behavior and neuroticism, but this result needs to be replicated in a bipolar disorder sample specifically. Again, one explanation that requires further exploration is that the experience of completed suicide in a family member may confer a risk for maladaptive and pervasive patterns of interpersonal relations that manifest as cluster C personality disorders. Alternatively, cluster C personality disorder may reflect an attenuated or residual form of an anxiety disorder (e.g., social phobia, obsessive-compulsive disorder). Comorbid anxiety has been associated with suicidality in other studies.[29,30] Unfortunately, we did not have a sufficient number of subjects with anxiety disorders to be able to do a meaningful analysis regarding the relationship between anxiety and cluster C personality disorders.

The primary limitation of this study is that family history of suicide was obtained without using standardized instruments. For that reason, only the effects of completed suicide in the family, and not other more ambiguous and difficult-to-collect data, such as suicidal ideation or attempts, were evaluated. Another limitation is that the present study did not ascertain or examine family history of suicide attempt. Subjects were recruited from a tertiary care setting with difficult-to-treat patients referred to the Bipolar Disorder Program of Barcelona and may not be representative of bipolar subjects in other community or non-tertiary settings. However, our program also provides clinical care to all bipolar disorder subjects residing in a specific catchment area in Barcelona, and those subjects were also included in the sample.

In summary, the findings of the present study provide further support for the assertion that family history of suicide has potentially important clinical implications for subjects with bipolar disorder. Family history of completed suicide is associated with greatly increased risk of suicidality in patients with bipolar disorder. Despite the

limitations of this study, present findings underscore the clinical importance of ascertaining family history of suicide and of providing early aggressive treatment and careful follow-up to this high-risk group.

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