

## Comparison of Women With Confirmed Versus Presumably Misdiagnosed Bipolar Disorder

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### ABSTRACT

**Objective:** Because bipolar disorder can be difficult to diagnose, we compared characteristics of women with confirmed versus presumably misdiagnosed bipolar disorder.

**Method:** This cohort study was conducted from July 2005 to January 2010 in the outpatient clinic of the Emory Women's Mental Health Program, Atlanta, Georgia. Young adult women (mean age = 32 years) who were either pregnant or planning to conceive and who reported having previous clinical diagnoses of bipolar disorder completed 2 independent diagnostic assessments: the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) and an evaluation by a perinatal mood-disorder expert who was masked to the SCID findings. We compared clinical characteristics of women with confirmed versus presumably misdiagnosed bipolar disorder by bivariate testing followed by multivariate logistic regression modeling.

**Results:** Of 199 participants, 141 (70.9%) had confirmed DSM-IV bipolar disorder on the basis of concordant assessments, 23 (11.6%) were considered misdiagnosed, and 35 (17.6%) who had discordant diagnostic assessments were excluded from further analysis. Multivariate modeling indicated that confirmed bipolar disorder was associated with a history of antidepressant-associated mania/hypomania (OR = 13.30; 95% CI, 3.32–53.20;  $P = .0003$ ), psychotic symptoms (OR = 12.40; 95% CI, 2.14–71.10;  $P = .005$ ), and sustained euthymia during mood-stabilizer treatment (OR = 4.53; 95% CI, 1.32–15.60;  $P = .02$ ); presumably misdiagnosed bipolar disorder was associated with childhood physical abuse (OR = 8.73; 95% CI, 2.33–32.70;  $P = .001$ ) and comorbid obsessive-compulsive disorder (OR = 7.26; 95% CI, 1.86–28.30;  $P = .004$ ).

**Conclusions:** Several clinical factors found to distinguish women with confirmed versus presumably misdiagnosed bipolar disorder may help to refine clinical diagnosis.

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Bipolar disorder can be difficult to diagnose accurately, despite distinctive clinical characteristics in typical adult cases. Some features of bipolar disorder can occur in other psychiatric disorders, including major depressive disorder, psychotic disorders, anxiety disorders, substance-use disorders, attention-deficit disorder, impulse-control disorders, and personality disorders<sup>1–7</sup>; in a variety of neuromedical conditions<sup>8,9</sup>; and in response to mood-elevating substances.<sup>8,10</sup> Consequently, bipolar disorder has a substantial risk of both underdiagnosis and overdiagnosis. The diagnosis has been overlooked in various clinical settings in up to 69% of adults with bipolar disorder,<sup>5,11,12</sup> and 45% of psychiatrists who were presented a case vignette of an acutely manic patient failed to identify bipolar disorder.<sup>13</sup> Many patients are not diagnosed with bipolar disorder for 5–10 years following its onset,<sup>14–17</sup> and 27.5% have been considered to have unipolar depression even after a correct diagnosis of bipolar disorder had been made.<sup>18</sup> Furthermore, patients with delayed or overlooked diagnoses of bipolar disorder are less likely to receive indicated treatment and may receive inappropriate treatment (particularly with antidepressants) that can exacerbate bipolar disorder, whereas those with incorrectly diagnosed bipolar disorder may receive unnecessary or inappropriate treatment. Accurate diagnosis of bipolar disorder is particularly important for women during reproductive years, owing to high risk of perinatal recurrence of bipolar disorder<sup>19–21</sup> as well as potential teratogenic and other adverse effects of treatment with psychotropic drugs during pregnancy.<sup>22</sup>

There have been few analyses of characteristics of young women with questionable diagnoses of bipolar disorder according to research diagnostic criteria. Accordingly, among women in their reproductive years who had a prior clinical diagnosis of bipolar disorder, we compared characteristics of those with confirmed versus unconfirmed and presumably misdiagnosed bipolar disorder.

### METHOD

Women who were referred by their primary-care physicians, obstetricians, or mental health care providers to the outpatient clinic of the Emory Women's Mental Health Program, Atlanta, Georgia, from July 2005 to January 2010 were evaluated for possible inclusion in a prospective study of the perinatal course of bipolar disorder. During initial telephone screening, women who were pregnant or planning to conceive and who reported having been previously diagnosed with bipolar disorder by a health care professional were scheduled for possible study enrollment. At an enrollment visit, all subjects provided written informed consent to participate. The study was approved by the Emory Institutional Review Board.

We employed 2 independent diagnostic assessment methods: (1) the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID),<sup>23</sup> a research instrument that identifies current and lifetime diagnoses, administered by a trained research interviewer (B.T.K., S.V.F., or N.J.M.) and (2) a clinical psychiatric diagnostic interview administered by an experienced perinatal mood-disorder psychiatrist (D.J.N. or Z.N.S.) who was masked to the results

- Accurate diagnosis of bipolar disorder in women prior to pregnancy is especially important for maximizing maternal and fetal well-being.
- Among young women previously diagnosed with bipolar disorder, a history of antidepressant-associated mania/hypomania provides particularly strong support for a diagnosis of bipolar disorder.
- Among young women previously diagnosed with bipolar disorder, early onset of the disorder and a history of substance use disorder complicate efforts to confirm the diagnosis.

of the SCID. Additional assessments included the collection of basic demographic, psychiatric, and medical-gynecologic data; a customized questionnaire (available from the authors upon request) to elicit details pertaining to the historical course of mood disorders and related treatment; and the self-report Childhood Trauma Questionnaire<sup>24</sup> that documents 5 categories of early trauma.

Participants for whom the independent SCID and the expert diagnostic assessments were concordant for lifetime *DSM-IV* bipolar disorder (type I, II, or not otherwise specified) were considered to have confirmed bipolar disorder; those with assessments concordant for the absence of bipolar disorder were presumed to have previously been misdiagnosed. Subjects for whom the SCID and the clinical interview were discordant for bipolar disorder were deemed diagnostically indeterminate and were compared with those who were concordant, but they were not included in the primary analyses comparing women with confirmed versus disconfirmed bipolar disorder diagnoses. We carried out a preliminary series of bivariate comparisons of demographic and clinical factors between the *confirmed* bipolar disorder group and the *presumably misdiagnosed* group using contingency table methods ( $\chi^2$  with  $df=1$ ). Factors with suggestive associations ( $P \leq .10$ ) with confirmed bipolar disorder diagnoses were evaluated by stepwise multivariate logistic regression modeling.

## RESULTS

### Subject Characteristics

The overall cohort of women with previous clinical diagnoses of bipolar disorder ( $N=199$ ) included 158 white subjects (79.4%), 26 African American subjects (13.1%), and 15 subjects with other racial-ethnic backgrounds (7.5%). The current mean age  $\pm$  SD was  $32.0 \pm 5.2$  years. Most patients were married ( $n=146$ , 73.4%), 39 (19.6%) had never been married, and 14 (7.0%) were divorced or separated. Many patients had completed college ( $n=123$ , 61.8%), 69 (34.7%) had completed high school or had some college education, and only 7 (3.5%) did not complete high school. Approximately

half of the subjects ( $n=100$ , 50.3%) were pregnant at the time of SCID assessment; the remainder were planning to conceive.

The SCID assessment and clinical diagnostic findings were concordant for 164 of the 199 women (82.4%), confirming *DSM-IV* bipolar disorder in 141 women (70.9%) and the absence of bipolar disorder in 23 women (11.6%). Diagnostic results were discordant for the remaining 35 women (17.6%), of whom 27 fulfilled *DSM-IV* criteria for bipolar disorder on the SCID only and 8 fulfilled *DSM-IV* criteria for bipolar disorder in the clinical assessment only.

### Comparisons of Subjects With Discordant and Concordant Diagnostic Assessments

All demographic and most clinical characteristics for the 164 concordantly diagnosed subjects were similar to the 35 excluded as diagnostically discordant. In addition, diagnostic concordance rates were similar whether subjects were pregnant (80.0%, 80 of 100) or not (84.9%, 84 of 99) at intake ( $\chi^2=0.81$ ,  $P=.37$ ). However, discordantly diagnosed subjects were more likely to report onset of mood disorders before age 20 (65.7% vs 47.0% for concordantly diagnosed;  $\chi^2_1=4.06$ ,  $P=.04$ ), less likely to report full interepisode recovery (40.0% vs 60.4%, respectively;  $\chi^2_1=4.88$ ,  $P=.03$ ), and more likely to fulfill *DSM-IV* criteria per the SCID for a lifetime history of alcohol abuse or dependence (51.4% vs 30.5%, respectively;  $\chi^2_1=5.62$ ,  $P=.02$ ), cannabis use (22.9% vs 9.8%, respectively;  $\chi^2_1=4.67$ ,  $P=.03$ ), or any substance use disorder (68.6% vs 38.4%, respectively;  $\chi^2_1=10.66$ ,  $P=.001$ ).

### Comparisons of Subjects With Confirmed Bipolar Disorder and Those Presumably Misdiagnosed

Bipolar disorder diagnostic types for the 141 women with confirmed bipolar disorder ranked as follows: bipolar I disorder (80.9%), bipolar II disorder (15.6%), and bipolar disorder not otherwise specified (3.6%) (Table 1). Rates of psychiatric comorbidities were high and similar in both groups, including 435 lifetime *DSM-IV* Axis I diagnoses in the 141 women with confirmed bipolar disorder (mean = 3.1 diagnoses per person) and 75 among the 23 presumably misdiagnosed women (mean = 3.3 diagnoses per person). The distribution of comorbidities for these groups also was similar (Table 1). Only obsessive-compulsive disorder was significantly more prevalent among the presumably misdiagnosed cases than among the confirmed cases: 34.8% versus 13.5% (Table 1).

There were no significant demographic differences between the confirmed and presumably misdiagnosed groups, but other contrasts were striking (Table 2). Ranked by statistical significance, findings more common among confirmed bipolar disorder subjects included (1) previous episodes of mania or hypomania during antidepressant treatment ( $P<.0001$ ), (2) most effective previous regimen included an FDA-approved mood stabilizer ( $P=.0002$ ), (3) sustained euthymia ( $\geq 12$  months) during mood-stabilizer treatment ( $P=.002$ ), and (4) previous psychotic symptoms ( $P=.007$ ). Findings more prevalent among presumably misdiagnosed

**Table 1. Principal and Comorbid Axis I Diagnoses Associated With Confirmed vs Presumably Misdiagnosed Bipolar Disorder (N = 164)**

Lifetime <i>DSM-IV</i> Axis I Disorder (by SCID assessment)	Confirmed Bipolar Disorder (n = 141)	Presumably Misdiagnosed Bipolar Disorder (n = 23)	$\chi^2$	P Value
Mood disorders, %				
Bipolar I disorder	80.9	NA		
Bipolar II disorder	15.6	NA		
Bipolar disorder not otherwise specified	3.6	NA		
Major depressive disorder	NA	91.3		
Dysthymic disorder	NA	4.4		
Any mood disorder	100.0	95.7		
Anxiety disorders, %				
Agoraphobia	5.7	0.0	1.37	.38
Generalized anxiety disorder	19.9	26.1	0.47	.58
Panic disorder	23.4	39.1	2.57	.11
Obsessive-compulsive disorder	13.5	34.8	6.52	.02
Posttraumatic stress disorder	33.3	34.8	0.02	.89
Social anxiety disorder	14.9	21.7	0.69	.54
Specific phobia	9.2	13.0	0.57	.70
Any anxiety disorder	65.3	78.3	1.52	.22
Substance dependence disorders, %				
Alcohol dependence	30.5	30.4	0.00	.99
Cannabis dependence	11.4	0.0	2.89	.13
Cocaine dependence	6.4	13.0	1.29	.38
Hallucinogen dependence	2.8	0.0	0.67	.64
Opioid dependence	2.1	0.0	0.50	1.00
Sedative-hypnotic dependence	4.3	0.0	1.02	.60
Stimulant dependence	2.8	0.0	0.67	.64
Any substance dependence disorder	39.0	34.8	0.15	.70
Eating disorders, %				
Anorexia nervosa	7.1	0.0	1.74	.36
Binge eating disorder	7.8	0.0	1.92	.23
Bulimia nervosa	8.5	8.7	0.00	1.00
Any eating disorder	22.7	8.7	2.36	.17

Abbreviations: NA = not applicable, SCID = Structured Clinical Interview for *DSM-IV* Axis I Disorders.**Table 2. Factors Associated With Confirmed vs Presumably Misdiagnosed Bipolar Disorder (N = 164)<sup>a,b</sup>**

Factor	Confirmed Bipolar Disorder (n = 141)	Presumably Misdiagnosed Bipolar Disorder (n = 23)	$\chi^2$	P Value
Course of previous mental illness, %				
Previous psychotic symptoms	42.6	13.0	7.28	.007
Previous treatment response, %				
Previous mania/hypomania with antidepressant	66.0	17.4	19.30	<.0001
Best regimen included FDA-approved mood stabilizer	83.0	47.8	14.30	.0002
Previous sustained euthymia ( $\geq 12$ mo) with mood stabilizer	61.0	26.1	9.78	.002
Best regimen included stimulant	3.6	13.0	3.84	.05
Obstetric-gynecologic history, %				
Current pregnancy not desired	3.6	19.4	11.50	.004
Previous sexually transmitted disease	17.0	34.8	3.97	.05
Childhood maltreatment, %				
Childhood history of physical abuse	17.9	47.8	10.30	.001
Childhood history of emotional neglect	13.4	38.1	7.91	.01
Childhood history of emotional abuse	26.1	47.6	4.07	.04
Other <i>DSM-IV</i> lifetime diagnoses per SCID, %				
Obsessive-compulsive disorder	13.5	34.8	6.52	.02

<sup>a</sup>Factors with suggestive but nonsignificant associations ( $P = .10$  to  $P > .05$ ) included the following: (a) previous sustained euthymia ( $\geq 12$  mo) without mood stabilizer ( $\chi^2 = 3.48$ ,  $P = .06$ ), (b) previous full interepisode recovery ( $\chi^2 = 3.19$ ,  $P = .07$ ), (c) best regimen included antidepressant therapy ( $\chi^2 = 3.48$ ,  $P = .07$ ), and (d) best regimen included a hypnotic ( $\chi^2 = 2.89$ ,  $P = .09$ ).

<sup>b</sup>Factors that were *not* significantly different ( $P > .10$ ) between subgroups included the following: (a) demographics (including current age, race, marital status, or education level); (b) age at onset or initial diagnosis of bipolar disorder or any mood disorder; (c) type of previous bipolar disorder diagnosis (bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified); (d) previous rapid cycling; (e) family history of bipolar disorder; (f) gynecologic history (including parity, premenstrual dysphoria, abortion, or current pregnancy status [including planning]); (g) childhood sexual abuse or physical neglect; (h) lifetime *DSM-IV* diagnosis of substance-use disorder, eating disorder, generalized anxiety disorder, panic disorder, social anxiety disorder, or posttraumatic stress disorder; (i) previous suicide attempt or psychiatric hospitalization; (j) best regimen included benzodiazepine therapy; and (k) lack of benefit from any previous treatment.

Abbreviations: FDA = US Food and Drug Administration, SCID = Structured Clinical Interview for *DSM-IV* Axis I Disorders.

**Table 3. Logistic Regression Modeling of Factors Associated With Confirmed Diagnosis of Bipolar Disorder<sup>a,b</sup>**

Factor	Odds Ratio (95% CI)	$\chi^2$	P Value
Previous antidepressant-associated mania/hypomania	13.30 (3.32–53.20)	13.40	.0003
No childhood history of physical abuse	8.73 (2.33–32.70)	10.30	.001
No lifetime history of obsessive-compulsive disorder	7.26 (1.86–28.30)	8.15	.004
Previous psychotic symptoms	12.40 (2.14–71.10)	7.92	.005
Previous sustained euthymia ( $\geq 12$ mo) with mood stabilizer	4.53 (1.32–15.60)	5.75	.02

<sup>a</sup>The log-likelihood for the model was 133 ( $\chi^2_5 = 54.3$ ,  $P < .0001$ ); Cox and Snell  $R^2 = 0.28$ ; Nagelkerke  $R^2 = 0.51$ ; the Hosmer and Lemeshow goodness-of-fit test indicated adequate fit ( $\chi^2_7 = 4.49$ ,  $P = .72$ ).

<sup>b</sup>Factors not associated with bipolar disorder diagnosis included the following: (a) previous best regimen included an FDA-approved mood stabilizer, antidepressant, hypnotic, or stimulant; (b) previous sustained euthymia ( $\geq 12$  mo) without a mood stabilizer; (c) previous full interepisode recovery; (d) childhood history of emotional abuse or emotional neglect; (e) current pregnancy not desired; and (f) previous sexually transmitted disease.

Abbreviation: FDA = US Food and Drug Administration.

subjects included (1) childhood history of physical abuse ( $P = .001$ ), (2) current pregnancy not desired ( $P = .004$ ), (3) childhood history of emotional neglect ( $P = .01$ ), (4) lifetime diagnosis of obsessive-compulsive disorder ( $P = .02$ ), (5) childhood history of emotional abuse ( $P = .04$ ), (6) most effective previous regimen included a stimulant ( $P = .05$ ), and (7) previous sexually transmitted disease ( $P = .05$ ).

In multivariate logistic regression modeling, 5 factors remained significantly and independently associated with confirmed bipolar disorder and are ranked by significance as follows: (1) previous antidepressant-associated mania or hypomania, (2) absence of childhood history of physical abuse, (3) absence of lifetime history of obsessive-compulsive disorder, (4) previous psychotic symptoms, and (5) previous sustained euthymia ( $\geq 12$  months) during mood-stabilizer treatment (Table 3).

## DISCUSSION

In evaluations of women of reproductive age who reported previous clinical diagnoses of bipolar disorder, several factors discriminated those with confirmed bipolar disorder versus presumably misdiagnosed bipolar disorder. Notably, and not unexpectedly, a history of psychosis, antidepressant-associated mania or hypomania, and sustained euthymia during mood-stabilizer treatment supported a confirmed diagnosis of bipolar disorder. However, childhood history of moderate to severe physical abuse and lifetime obsessive-compulsive disorder were associated with presumably misdiagnosed bipolar disorder. These factors are readily ascertained in a clinical assessment and so may aid in supporting the accuracy of a clinical diagnosis of bipolar disorder if the present sample is representative of other patients.

A unique strength of this study is its use of 2 independent diagnostic assessments, bolstering confidence in the

confirmation or rejection of previous clinical diagnoses of bipolar disorder. The observed rate of apparently misdiagnosed bipolar disorder (11.6%) was considerably lower than rates of 33%–57% in previous reports.<sup>5–7,12</sup> This disparity may be a consequence of prescreening that eliminated women who did not report a prior clinical history of bipolar disorder diagnosis in addition to the exclusion of 17.6% of the current sample due to discordant, and thereby indeterminate, diagnostic results produced by the 2 independent diagnostic assessments, or a total of 29.2% with unconfirmed diagnosis of bipolar disorder.

This study is limited by including a demographically and clinically limited range of women of reproductive age near or during pregnancy who presented to a tertiary-care, perinatal psychiatry clinic. It is therefore possible that the reported findings may not generalize to women in other settings, or to men. In addition, targeted recruitment based on previous clinical diagnoses of bipolar disorder precluded assessment of underdiagnosis of bipolar disorder and could only address apparent overdiagnosis. Furthermore, historical information was determined by patient self-report, without verification from additional sources, such as medical records or corroboration by relatives or friends. Despite these limitations, the current findings provide suggestions for promoting more accurate clinical diagnoses of bipolar disorder in young adult women, with the result of more appropriate treatment.

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