Risk Factors Associated With Antidepressant Exposure and History of Antidepressant-Induced Mania in Bipolar Disorder

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ABSTRACT

Objective: Despite their widespread use in bipolar disorder, there is controversy surrounding the inclusion of antidepressant medications in the disorder's management. We sought to identify which demographic, socioeconomic, and clinical factors are associated with antidepressant exposure in bipolar disorder and which bipolar disorder patients are most likely to report a history of antidepressant-induced mania (AIM) when exposed to antidepressants.

Methods: Our study included subjects with bipolar I disorder (n = 309), bipolar II disorder (n = 66), and bipolar disorder not otherwise specified (n = 27) and schizoaffective disorder, bipolar type (n = 14), from a longitudinal, community-based study. Subjects were evaluated using the Diagnostic Interview for Genetic Studies, modified for *DSM-IV* criteria. We applied multivariate logistical regression modeling to investigate which factors contribute to antidepressant exposure in bipolar disorder patients. We also used a logistic regression modeling approach to determine which clinical factors in bipolar disorder patients are associated with a history of AIM. Data were gathered from February 2006 through December 2010.

Results: Our results suggest that the risk factors most strongly associated with antidepressant exposure are female sex (OR = 2.73, *P* = .005), older age (OR = 1.03, *P* = .04), greater chronicity of illness (OR = 2.29, *P* = .04), and, to a lesser extent, white race (OR = 0.44, *P* = .051). Factors associated with reduced antidepressant exposure include history of affective psychosis (OR = 0.36, *P* = .01) and a greater number of previous manic episodes (OR = 0.98, *P* = .03). In subjects who reported a history of AIM, regression analysis revealed that the only statistically significant factor associated with AIM history was female sex (OR = 3.74, *P* = .02).

Conclusions: These data suggest that there are certain identifiable factors associated with antidepressant exposure in bipolar disorder patients, and some of these, specifically female sex, are also associated with a history of AIM. These data may be useful in designing prospective trials to identify interventions that can reduce the risk of this adverse outcome.

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Bipolar disorder is an episodic mood disorder characterized by fluctuations in mood, energy level, and sleep patterns. Treatment requires mood-stabilizing medications, such as lithium, valproate, or atypical antipsychotics, which generally control manic symptoms more effectively than depressive symptoms.[1] Depressive symptoms can be difficult to treat in bipolar disorder, as they are often treatment-resistant and debilitating. Treatment guidelines support the use of antidepressant medications in bipolar disorder only in the context of a mood-stabilizing agent,[2] although it is notable that available treatment guidelines vary substantially.[3] A survey of Americans with bipolar disorder[4] found that antidepressants not only are the single most-prescribed class of medications in bipolar disorder, outranking first-line mood-stabilizing medications, but also are often prescribed as initial monotherapy despite having no US Food and Drug Administration approval as monotherapy for bipolar disorder and significant controversy surrounding their safety and efficacy in these diseases; in that survey, antidepressants were found to be the first-choice medication twice as often as mood stabilizers.[4]

The development of manic-type symptoms after initiation of treatment with antidepressant medication has been commonly described as antidepressant-induced mania (AIM).[5,6] Antidepressant-induced mania is thought to be most common in bipolar disorder patients who take antidepressants without a concomitant mood stabilizer, although it can occur while a patient is taking mood-stabilizing medications.[6,7] Notably, AIM does not occur in all bipolar disorder patients who take antidepressants, and it is believed that some patients benefit from the use of antidepressants for the treatment of bipolar depression, especially in the context of ongoing treatment with mood stabilizers.[8]

To our knowledge, there are no evidence-based risk stratification algorithms to assist clinicians in determining who is most likely to develop AIM with antidepressant use. One study from Gorwood and colleagues[7] suggests that among bipolar disorder patients already treated with a mood stabilizer (defined as lithium, valproate, or carbamazepine), the best predictors of AIM were the patient's individual cumulative number of any mood episodes, but particularly the number of manic episodes, or a previous

Clinical Points

- Depression is a common feature of bipolar disorder, and the use of antidepressants in bipolar disorder treatment is controversial.
- For patients with bipolar disorder, female sex increases the risk of antidepressant-induced mania.

experience of AIM. Subjects in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial[9] were also found to have an increased risk of AIM if they had a previous experience of AIM, which occurred more often during treatment with tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), or bupropion compared to monoamine oxidase inhibitors (MAOIs) or electroconvulsive therapy (ECT). Other risk factors identified in STEP-BD included younger age and multiple previous antidepressant trials.[9] Along with a previous AIM episode, TCAs were also associated with higher risk of AIM in a naturalistic study of bipolar disorder.[10] Goldberg and Truman[6] performed a systematic review including both published literature and unpublished data which suggested that the rate of AIM in bipolar disorder patients is around 20%–40% and also concluded that previous AIM episodes and possibly TCA treatment are linked with higher AIM risk. However, this finding is not without controversy, as natural cycling occurs in bipolar disorder, which may confound findings that TCAs increase manic episodes.[11] There are also data to suggest that the bipolar I subtype itself is a risk factor for AIM,[12] whereas in the bipolar II subtype, it is possible that antidepressant monotherapy does not increase switch rates when compared to either lithium monotherapy or combined lithium-antidepressant therapy.[13]

Here, we present data from a naturalistic, longitudinal, observational study of bipolar disorder[14] showing the proportion of study subjects reporting a history of AIM, the variables associated with antidepressant exposure in this population, and the risk factors associated with a report of positive AIM history. Although the term *AIM* implies causation, this study is not designed to assess causation, and we use this term only to avoid further confusion. In our study, *AIM* refers to the onset of self-reported symptoms of mania or hypomania occurring shortly after initiation of treatment with antidepressants.

METHODS

Data were collected as part of a larger study approved by the University of Michigan Institutional Review Board (IRBMED). This larger study is a longitudinal naturalistic observational study of bipolar disorders. Recruitment methods and selection criteria are described in detail elsewhere.[14–17] Briefly, we recruited adults (aged at least 18 years) with a history of bipolar spectrum disorder, excluding patients with psychiatric illness secondary to medical conditions or gross intellectual impairment, from February 2006 through December 2010. All participants provided informed consent before enrolling in the study. All participants were clinically interviewed using the Diagnostic Interview for Genetic Studies (DIGS), modified for *DSM-IV* criteria.[18] We included subjects with a diagnosis of bipolar disorder of any type, including bipolar I disorder (BP-I), bipolar II disorder (BP-II), and bipolar disorder not otherwise specified (BP-NOS) and schizoaffective disorder, bipolar type (SA-BP), using a consensus best estimate diagnosis procedure as previously described.[19] Medical records were also reviewed when available. The following variables were obtained directly from baseline DIGS evaluation: demographic variables, age at onset of mood episodes, numbers of mood episodes, physical comorbidities, presence of rapid cycling, history of affective psychosis, history of suicide attempt, history of mixed episodes, family history of bipolar disorder, hospitalization history, and ECT treatment history. Years of illness were calculated from age at onset of first mood episode regardless of valence. Chronicity of substance abuse and affective disorder was inferred from DIGS data, such that a subject was considered to have chronic symptoms if symptoms were present longer than they were absent over the course of the subject's lifetime. In regards to antidepressant exposure, subjects were divided into 2 groups: those who reported any lifetime exposure to antidepressants (regardless of whether they were currently taking an antidepressant medication) and those who had never received any antidepressant treatment aside from psychotherapy. For AIM risk, we excluded all subjects who had never received antidepressant treatment (as these subjects by definition could not have had AIM) and then grouped the remaining subjects into those who reported a lifetime history of at least 1 AIM episode and those who reported no previous experience of AIM. The DIGS instrument includes an item asking whether the subject recalls experiencing a manic or hypomanic episode shortly after antidepressant initiation, ECT, or a course of light therapy; those who answered "yes" or "no" were included in the AIM or non-AIM groups, respectively. If the subjects were unsure whether they had experienced mania or hypomania after receiving antidepressant treatment, we excluded them from the analysis.

Statistical Analysis

Descriptive analyses were conducted for patients' demographics, clinical factors, and comorbidities. Bivariate analyses, using χ^2 for categorical variables and t tests for continuous variables, were performed to compare differences between groups. We then performed multiple variable logistic regression modeling to examine factors that might predict antidepressant prescription. For regression modeling, we included factors from the bivariate analyses that showed statistical significance at $P < .05$ as well as demographic factors. All analyses were performed using SAS 9.4 (Cary, NC). We performed complete case analysis; in cases for which the predictor variables of interest were

Table 1. Study Subject Demographic and Clinical Data[a]

Characteristic	Overall (N = 416)	BP-I (n = 309)	BP-II (n = 66)	BP-NOS (n = 27)	Schizoaffective (n = 14)	χ^2/F	*P* Value
Female	270 (64.9)	191 (61.8)	47 (71.2)	22 (81.5)	10 (71.4)	5.9	.11
White	341 (81.9)	258 (83.5)	53 (80.3)	18 (66.7)	12 (85.7)	5.0	.17
Age, mean (SD), y	40.5 (13.2)	40.1 (13.0)	42.6 (13.7)	37.7 (13.2)	43.6 (14.1)	1.3	.27
≥ 1 lifetime antidepressant prescription	365 (87.7)	260 (84.1)	66 (100)	27 (100)	12 (85.7)	16.8	< .0001
Years of illness, mean (SD)	20.3 (49.0)	18.8 (56.2)	26.7 (13.6)	20.9 (13.6)	23.6 (13.1)	0.5	.68

[a]Data shown as n (%) unless otherwise noted.
Abbreviations: BP = bipolar disorder, NOS = not otherwise specified.

Table 2. Bivariate Statistics of Clinical Features of Subjects Who Have and Who Have Not Been Exposed to Antidepressants[a]

Characteristic	Overall (N = 416)	History of AD Exposure (n = 365)	No AD Exposure (n = 51)	χ^2/t	*P* Value
Female	270 (64.9)	250 (68.5)	20 (39.2)	16.8	< .0001
White	341 (82.0)	304 (83.3)	37 (72.5)	3.5	.06
Age, mean (SD), y	40.5 (13.2)	41.2 (13.0)	35.2 (13.4)	−3.1	.002
Age at onset of mania, mean (SD), y	24.6 (9.9)	25.0 (10.4)	22.7 (7.4)	−1.9	.05
No. of manic episodes, mean (SD)	9.2 (25.1)	9.4 (24.7)	8.4 (28.2)	−0.3	.80
Age at onset of depression, mean (SD), y	19.1 (9.0)	18.8 (8.9)	21.2 (9.1)	1.7	.08
No. of depressive episodes, mean (SD)	23.9 (47.5)	25.9 (49.2)	9.7 (29.1)	−3.4	.001
Age at onset of hypomania, mean (SD), y	21.6 (9.8)	21.6 (9.8)	21.9 (9.7)	0.2	.88
No. of hypomanic episodes, mean (SD)	30.2 (65.6)	32.9 (69.2)	10.4 (21.5)	−4.7	< .0001
Years of illness, mean (SD)	20.3 (49.0)	20.9 (51.9)	15.6 (14.8)	−1.6	.11
No. of physical comorbidities, mean (SD)	0.6 (0.8)	0.7 (0.8)	0.5 (0.8)	−1.3	.20
Overweight	202 (48.6)	187 (51.2)	15 (29.4)	8.5	.003
Alzheimer's disease	0 (0)	0 (0)	0 (0)	…	…
Epilepsy	21 (5.0)	17 (4.7)	4 (7.8)	0.9	.33
Head injury	97 (23.3)	85 (23.3)	12 (23.5)	0.002	.96
Migraine	127 (30.5)	120 (32.9)	7 (13.7)	7.7	.005
Stroke	5 (1.2)	4 (1.1)	1 (2.0)	0.3	.59
Fibromyalgia	16 (3.8)	14 (3.8)	2 (3.9)	0.001	.97
Affective psychosis	224 (53.8)	183 (50.1)	41 (80.4)	16.5	< .0001
Rapid cycling	143 (34.4)	134 (36.7)	9 (17.6)	7.2	.007
Suicide attempt	169 (40.6)	158 (43.3)	11 (21.6)	9.4	.002
Chronicity of substance abuse	230 (55.3)	205 (56.2)	25 (49.0)	0.9	.34
Chronicity of affective disorder	244 (58.6)	228 (62.5)	16 (31.4)	20.8	< .0001
Mixed episode	110 (26.4)	97 (26.6)	13 (25.5)	0.03	.86
First-degree relative with bipolar disorder	158 (38.0)	140 (38.4)	18 (35.3)	0.2	.67
Mood-related hospitalization	318 (76.4)	276 (75.6)	42 (82.4)	1.1	.28
ECT	33 (7.9)	27 (7.4)	6 (11.8)	1.2	.27

[a]Data shown as n (%) unless otherwise noted.
Abbreviations: AD = antidepressant, ECT = electroconvulsive therapy.

missing from the assessment data, the subjects were removed from regression analyses. We considered $P \leq .05$ as significant and $P > .05$ but < 0.1 as marginal.

RESULTS

Our sample consists primarily of subjects with BP-I (n = 309; 74.3%) but also includes subjects with BP-II (n = 66; 15.9%), BP-NOS (n = 27; 6.5%), and SA-BP (n = 14; 3.4%). The vast majority of the subjects in our sample (88%) had been prescribed antidepressants at some point in their history, including 84% of BP-I subjects, 100% of both BP-II and BP-NOS subjects, and 85% of SA-BP subjects. Subjects in the different bipolar disorder subgroups were similar in terms of sex, race, age, and total years of illness (Table 1). Although most subjects had been exposed to antidepressants at least once, a statistically greater proportion of BP-II and BP-NOS subjects were exposed compared to both BP-I and SA-BP ($P < .0001$) (Table 1).

We then looked for differences in the characteristics of patients who had been exposed to antidepressants. For these analyses, all bipolar disorder subgroups were pooled. As shown in Table 2, subjects exposed to antidepressants were more likely to be female (68.5% of antidepressant-exposed subjects vs 39.2% of unexposed subjects, $P < .0001$) and older (41.2 years vs 35.2 years of age, $P = .002$). Notably, there was no difference in years of illness between these 2 groups (20.9 years vs 15.6 years, $P = .11$), although more antidepressant-exposed subjects described their illness as chronic (greater time in episode than in remission, 64.8%) than did subjects never exposed (31.4%, $P < .0001$). In our pooled sample, patients who had taken antidepressants were marginally more likely to be white (83.3% vs 72.6%, $P = .06$), have a later age at onset of manic episodes (25.0 years vs 22.7 years, $P = .05$), and have an earlier age at onset of depressive episodes (18.8 years vs 21.2 years, $P = .08$). Patients exposed to antidepressants had a significantly greater lifetime number of episodes of depression (25.9 vs 9.7, $P = .001$)

and higher lifetime number of hypomanic episodes (32.9 vs 10.4, $P<.0001$), but no difference in lifetime number of manic episodes (9.4 vs 8.4, $P=.80$). Patients who had taken antidepressants were also more likely to be overweight (51.2% vs 29.4%, $P=.003$), have migraines (32.9% vs 13.7%, $P=.005$), and experience rapid cycling (36.7% vs 17.7%, $P=.007$). Patients who had taken antidepressants were also more likely to have attempted suicide in the past (43.3% vs 21.6%, $P=.002$) and less likely to have episodes of affective psychosis (50.1% vs 80.4%, $P<.0001$).

We then performed multivariate logistical regression modeling to determine which of the aforementioned factors were independent predictors for being prescribed an antidepressant, since some of the factors identified in bivariate analysis may be statistically related. Of the 416 subjects in our pooled group, 42 were excluded due to lack of data for at least 1 of the variables in our hypothesized model. Variables analyzed in the model included age; race; sex; being overweight; rapid mood cycling; history of affective psychosis; number of episodes of depression, mania, or hypomania; migraine; chronicity of affective disorder; and history of suicide attempts. Of those factors, regression analysis showed that the following contributed positively and significantly to antidepressant prescription (Table 3): older age (OR = 1.03; 95% CI, 1.001–1.059), being female (OR = 2.73; 95% CI, 1.348–5.534), and chronicity of affective disorder (OR = 2.29; 95% CI, 1.029–5.092). Both a personal history of affective psychosis (OR = 0.357; 95% CI, 0.160–0.795) and a greater number of manic episodes (OR = 0.984; 95% CI, 0.969–0.999) were significantly associated with a lower likelihood of being prescribed an antidepressant. Racial identity other than white was also associated with lower likelihood of antidepressant prescription, although the strength of the association was marginal (OR = 0.442; 95% CI, 0.195–1.002).

We then compared subjects who reported a positive or negative history of AIM, limiting our analysis to those who had ever been exposed to an antidepressant. In our sample, 365 subjects reported exposure to antidepressants, of whom 19 were excluded due to missing responses, resulting in a final sample size of 346. In total, 10.7% of our sample reported an episode of AIM in their lifetime (37 of the total 346) (Table 4). Bivariate statistics for our pooled bipolar disorder sample (Table 4) revealed that subjects who

Table 3. Multivariate Logistic Regression Modeling of Risk Factors for Being Exposed to Antidepressants

Age	1.03 (1.00–1.06)	.045
Nonwhite	0.44 (0.20–1.00)	.051
Female	2.73 (1.35–5.53)	.005
Overweight	1.66 (0.78–3.54)	.186
Rapid cycling	1.49 (0.59–3.75)	.401
History of affective psychosis	0.36 (0.16–0.80)	.012
No. of manic episodes	0.98 (0.97–1.00)	.034
No. of depressive episodes	1.01 (1.00–1.03)	.177
No. of hypomanic episodes	1.01 (0.99–1.02)	.449
Migraine	1.80 (0.71–4.55)	.218
Chronicity of affective disorder	2.29 (1.03–5.09)	.042
History of suicide attempt	1.63 (0.72–3.71)	.244

Abbreviations: CI = confidence interval, OR = odds ratio.

Table 4. Bivariate Statistics of Clinical Features of Subjects Who Have or Have Not Reported a History of AIM in Response to Antidepressant Exposure[a]

Characteristic	Overall (N = 346)	AIM (n = 37)	No AIM (n = 309)	χ^2	*P* Value
Female	241 (69.7)	32 (86.5)	209 (67.6)	5.6	.01
White	287 (82.9)	32 (86.5)	255 (82.5)	0.4	.54
Age, mean (SD), y	41.0 (13.1)	36.2 (11.8)	41.6 (13.1)	2.4	.01
Age at onset of mania, mean (SD), y	24.9 (10.4)	25.4 (12.1)	24.9 (10.2)	−0.2	.80
No. of manic episodes, mean (SD)	9.4 (24.9)	3.6 (5.2)	10.1 (26.3)	3.7	.0003
Age at onset of depression, mean (SD), y	18.6 (8.9)	17.1 (8.6)	18.7 (8.9)	1.0	.30
No. of depressive episodes, mean (SD)	25.9 (49.4)	17.9 (33.5)	26.9 (50.9)	1.4	.15
Age at onset of hypomania, mean (SD), y	21.5 (9.7)	21.5 (12.2)	21.5 (9.4)	−0.02	.98
No. of hypomanic episodes, mean (SD)	32.5 (68.3)	36.2 (59.6)	32.1 (69.4)	−0.3	.73
Years of illness, mean (SD)	20.9 (53.3)	19.9 (13.1)	21.0 (56.3)	0.3	.77
No. of physical comorbidities, mean (SD)	0.7 (0.8)	0.7 (0.8)	0.6 (0.8)	−0.7	.51
Overweight	175 (50.6)	17 (45.9)	158 (51.1)	0.4	.55
Alzheimer's disease	0 (0)	0 (0)	0 (0)	…	…
Epilepsy	16 (4.6)	3 (8.1)	13 (4.2)	1.1	.28
Head injury	78 (22.5)	11 (29.7)	67 (21.7)	1.2	.26
Migraine	115 (33.2)	11 (29.7)	104 (33.7)	0.2	.63
Stroke	3 (0.9)	1 (2.7)	2 (0.6)	1.6	.20
Fibromyalgia	13 (3.8)	1 (2.7)	12 (3.9)	0.1	.72
Affective psychosis	169 (48.8)	15 (40.5)	154 (49.8)	1.1	.28
Rapid cycling	130 (37.6)	14 (37.8)	116 (37.5)	0.001	.97
Suicide attempt	150 (43.4)	18 (48.6)	132 (42.7)	0.4	.53
Chronicity of substance abuse	196 (56.6)	21 (56.8)	175 (56.6)	0.03	.87
Chronicity of affective disorder	216 (62.4)	23 (62.2)	193 (62.5)	0.01	.93
Mixed episode	94 (27.2)	12 (32.4)	82 (26.5)	0.6	.44
First-degree relative with bipolar disorder	136 (39.3)	12 (32.4)	124 (40.1)	0.8	.36
Mood-related hospitalization	261 (75.4)	27 (73.0)	234 (75.7)	0.1	.71
ECT	25 (7.2)	0 (0)	25 (8.1)	3.2	.07

[a]Data shown as n (%) unless otherwise noted.
Abbreviations: AIM = antidepressant-induced mania, ECT = electroconvulsive therapy.

Table 5. Multivariate Logistical Regression Modeling of Risk Factors Associated With a History of AIM

Variable	OR (95% CI)	*P* Value
Age	0.98 (0.96–1.01)	.115
Nonwhite	0.78 (0.27–2.22)	.638
Female	3.74 (1.22–11.41)	.021
Overweight	0.73 (0.33–1.58)	.420
Bipolar II disorder	0.50 (0.17–1.50)	.216
Rapid cycling	1.03 (0.44–2.40)	.954
History of affective psychosis	0.76 (0.35–1.66)	.495
No. of mania episodes	0.96 (0.91–1.01)	.130
No. of depression episodes	1.00 (0.99–1.01)	.824
No. of hypomania episodes	1.00 (1.00–1.01)	.331
Migraine	0.73 (0.32–1.62)	.433
Chronicity of affective disorder	1.05 (0.46–2.44)	.904
History of suicide attempt	1.20 (0.55–2.61)	.650

Abbreviations: AIM = antidepressant-induced mania, CI = confidence interval, OR = odds ratio.

experienced AIM after taking an antidepressant were more likely to be female (86.5% in the AIM group vs 67.6% in the non-AIM group, $P = .01$) and younger (mean age of 36.2 years in AIM group vs 41.6 years in non-AIM group, $P = .01$) and had fewer lifetime manic episodes (3.6 in AIM group vs 10.1 in non-AIM group, $P = .0003$). They were marginally less likely to have undergone ECT (0% in AIM group vs 25% in non-AIM group, $P = .07$).

We again performed multivariate logistical regression modeling to determine which factors were independent predictors for experiencing AIM after exposure to an antidepressant (Table 5). We included the larger set of factors from the previous logistic regression in this analysis because we wanted to examine the role of factors associated with antidepressant prescription to see if they were also associated with AIM (even if they were not statistically significant by bivariate analysis). We also included the diagnosis of bipolar disorder type II as a factor because all subjects with that diagnosis had been prescribed an antidepressant and we wanted to ensure that did not skew our findings. For logistical modeling, an additional 34 subjects were removed for missing data, resulting in a final sample size of 312. After adjustment for patient characteristics and clinical factors, the only variable in the model statistically associated with higher odds of a history of AIM was female sex. In our sample, female subjects were 3.74 times more likely to have a history of AIM than male subjects (OR = 3.74; 95% CI, 1.22–11.41) independent of all other demographic and clinical variables in the model.

DISCUSSION

In this retrospective study of bipolar disorder patients, we found the factors associated with antidepressant exposure were older age, female sex, a negative history for affective psychosis, lower number of manic episodes, and greater chronicity of bipolar illness. Being white was marginally associated with antidepressant exposure. We also found that among the variables included in our study, female sex was the only factor associated with a reported history of AIM.

Antidepressants are a mainstay of mood disorder treatment, but their use in bipolar disorder has been controversial due to concerns about AIM.[6] However, depressive episodes are common in bipolar disorder and are associated with significant risks, including suicide, for which reason antidepressants are often prescribed for bipolar depression.[8] Our results suggest that there are specific differences between bipolar disorder patients who are prescribed antidepressants and those who are not. In our study, patients who were female and older and had greater chronicity of illness were more likely to be prescribed an antidepressant, whereas patients with greater numbers of manic episodes and a history of affective psychosis were less likely. At a marginal level, white race was also associated with antidepressant exposure. Interestingly, of all the factors included in our multivariate regression modeling, only female sex was associated with history of AIM after exposure to antidepressants. Ours is the first study to find an association between female sex and history of AIM. Other studies have found that, in bipolar I disorder, the first episode for women tends to be depression rather than mania[20]; this fact may contribute to female patients' having higher rates of AIM since women may be more likely to present with depressive rather than manic symptoms at initial presentation. Azorin and colleagues[20] also noted that in men, the first episode of bipolar disorder tends to be mania, which can help clarify diagnosis and may make prescription of an antidepressant less likely. Misdiagnosis often leads bipolar disorder patients to be treated with antidepressants but not mood stabilizers,[21] which may contribute to high rates of antidepressant prescriptions in bipolar disorder. In our sample, bipolar disorder patients with psychosis and more frequent manic episodes had less exposure to antidepressants. Given the concerns voiced in the literature regarding the use of antidepressants in bipolar disorder, this finding may reflect that prescribers were more hesitant to prescribe antidepressants to these patients, as they were more confident in the diagnosis of bipolar disorder.

Our findings about the higher risk of AIM in female patients may reflect that bipolar disorder may manifest differently in women and that women may experience treatment side effects differently from men. For example, women may experience greater severity of bipolar depression than their male counterparts,[22] and some studies[23] have shown that depressive mood polarity is more likely in female than in male bipolar disorder patients. In another study,[24] women with bipolar disorder reported poorer sleep quality than men, and, in women only, poorer sleep quality predicted increased severity and frequency of depression, increased severity and variability of mania, and increased frequency of mixed episodes at 2-year follow-up. Kriegshauser and colleagues[25] found that alcohol abuse in bipolar disorder was greater in men than women, while women were more distressed by weight gain as a side effect of medication. Another study[26] found that although more male than female bipolar disorder patients have a lifetime

history of alcohol dependence, the risk of having alcohol dependence is actually higher for female bipolar disorder patients than male patients and is also associated with history of polysubstance use in women. There is also evidence that women have different medical and psychiatric comorbidities from men, including increased rates of posttraumatic stress disorder, eating disorders, and thyroid dysfunction, while men have higher rates of legal problems.[27] Women may experience other differences in bipolar disorder treatment, including differing management of comorbidities and medication side effects.[28] These differences could result in reporting different problems to physicians, which may ultimately lead to different treatment plans. However, at least 1 group[29] examining Swedish outpatients during 2004–2011 found that the outpatient treatments for men and women differed significantly, with women being prescribed more antidepressants and psychotherapy while men were more frequently prescribed lithium; these differences could not be explained by differences in severity of illness or other charted clinical features. These data, along with our own, support the idea that treatment decisions made by health care providers may be influenced by patients' sex and gender separate from considerations about the illness itself. In our sample, women not only were more likely to be prescribed antidepressants, but also had an increased likelihood of reporting a history of AIM after antidepressant exposure. Although our study was not specifically designed to clarify this issue, one concern our data raise is that bipolar disorder is not diagnosed as accurately in women as in men, leading to less than optimal treatment.

Our data provide additional support for the idea that there are interactions between patient demographic factors, illness features, and the likelihood that a patient will be treated with an antidepressant. Our study is the first to identify female sex as a risk factor for having a history of AIM. Another recent study also supports the idea that AIM risk factors differ between men and women: Scott and colleagues[30] found that men with a history of suicide attempts, comorbid alcohol or substance use disorder, and more depressive episodes were at higher risk of AIM whereas women with thyroid disease, a family history of bipolar type 1, and depressive episode at illness onset were more likely to experience AIM. That study did not find a difference in AIM rates between men and women. However, there were several major differences between our study sample and that of Scott et al,[30] most notably the definition of "non-AIM subjects." Scott et al limited their non-AIM group to subjects who had a previous depressive episode treated with an antidepressant without a coprescribed mood stabilizer, whereas our non-AIM group included those who had been prescribed an antidepressant regardless of other coprescribed medicines. Therefore, we included all people at risk, whereas their group was restricted to subjects considered to be at highest risk for AIM. Their study also restricted their analysis to risk factors identified in previous studies and therefore did not include some of the factors we included.

Limitations include the fact that this is a retrospective study in which subjects were asked to remember their own medication and health histories, and such information is subject to recall bias. When possible, we corroborated historical information from subjects with their medical records, but this was not possible in all cases. Additionally, given the retrospective nature of the study, we cannot rule out that patients who were considered by their clinicians to be at particularly high risk for AIM (eg, those who cannot tolerate mood stabilizers, those with rapid cycling subtype, those with history of mixed episodes) were not prescribed antidepressants as often, and therefore the risk in our sample does not reflect the true risk of AIM in all bipolar disorder patients. To the extent that we can compare our results to the literature, the lifetime prevalence of AIM in our study (10.7%) is within the range of AIM prevalence reported in other studies (3%–44% depending on study design).[9,30–36] Given the small number of subjects who reported a history of AIM, we may necessarily be limited in identifying risk factors. In an effort not to miss potential factors related to AIM, we did not correct for multiple testing in our bivariate analyses. This choice reduces type II errors at the cost of potential false-positive findings. However, by using logistic regression in the second part of our analyses, we reduced the likelihood of spurious results by reducing the statistical significance of factors that are highly associated with each other. A final consideration is that definitions of AIM vary widely across studies, and there is no consensus about what factors differentiate between AIM and the natural cycling of bipolar illness.[6] Our definition of AIM is broad in the sense that we included all mania or hypomania episodes that occurred after antidepressant exposure, light therapy, or ECT, and we did not limit the symptom onset window because it is unclear what onset window (eg, 7 days versus 30 days after antidepressant exposure) qualifies as "true" AIM.

Ultimately, the major question about whether antidepressants represent a greater risk than benefit for bipolar disorder patients remains open. Although some studies[31] have suggested that rates of AIM are increased in bipolar disorder patients on antidepressant monotherapy, alternative analyses[37] of these same data have been interpreted as evidence that antidepressant monotherapy does not increase rates of AIM (see also the response to this alternative analysis[38]). One study[34] from the STEP-BD cohort found that 21.3% of subjects experienced a mood transition directly from depression to a manic, hypomanic, or mixed state without intervening euthymia during the study period (1999–2005), and this rate did not appear to be influenced significantly by whether or not the subjects had recently started an antidepressant. Additionally, some data indicate that those whose initial manic or hypomanic episodes occurred after antidepressant treatment are at lower risk for recurrent episodes compared to those whose initial episodes were spontaneous,[39,40] suggesting that people who experience AIM may have a different course of illness from those with spontaneous mania or hypomania.

Therefore, the potential risks and benefits of antidepressants need to be taken into consideration along with individual patient symptoms, medical comorbidities, and preferences. Bipolar illness itself is dynamic, and treatment planning must include weighing whether a potential negative outcome (AIM) might be a tolerable risk in the attempt to manage a depressive episode. While these data cannot predict with precision which patients will or will not develop AIM on an individual basis, our results support the consideration of sex in the design of studies targeted toward AIM, the development of clinical prediction tools for AIM, and for potential efforts to prevent this adverse outcome.

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