Self-Reported History of Manic/Hypomanic Switch Associated With Antidepressant Use: Data From the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

Christine J. Truman, M.D.; Joseph F. Goldberg, M.D.; S. Nassir Ghaemi, M.D., M.P.H.; Claudia F. Baldassano, M.D.; Stephen R. Wisniewski, Ph.D.; Ellen B. Dennehy, Ph.D.; Michael E. Thase, M.D.; and Gary S. Sachs, M.D.

Objective: Antidepressant safety and efficacy remain controversial for the treatment of bipolar depression. The present study utilized data from the National Institute of Mental Health Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) to examine the prevalence and clinical correlates of self-reported switch into mania/hypomania during antidepressant treatment.

Method: Antidepressant treatment histories were examined from intake assessments for the first 500 subjects enrolled into the STEP-BD between November 1999 and November 2000. Affective switch was defined as a report of mania, hypomania, or mixed episodes within the first 12 weeks of having started an antidepressant. Demographic and clinical characteristics were compared for subjects with or without a history of acute switch during antidepressant treatment.

Results: Among the 338 subjects with prior antidepressant treatment and complete data on switch event outcomes, 44% reported at least 1 such occurrence. Patients with a shorter duration of illness (odds ratio [OR] = 1.02, 95% CI = 1.01 to 1.04) and a history of multiple antidepressant trials (OR = 1.73, 95% CI = 1.38 to 2.16) were more likely to report a history of switch than other patients. A significantly increased risk for affective polarity switch was identified in patients who had ever switched to mania/hypomania while taking tricyclic antidepressants (OR = 7.80, 95% CI = 1.56 to 28.9), serotonin reuptake inhibitors (OR = 3.73, 95% CI = 1.98 to 7.05), or bupropion (OR = 4.28, 95% CI = 1.72 to 10.6). Switch was less common during treatment with electroconvulsive therapy or monoamine oxidase inhibitors than other antidepressants.

Conclusions: Antidepressants are associated with the potential risk for treatment-emergent mania or hypomania, particularly in bipolar patients with short illness duration, multiple past antidepressant trials, and past experience of switch with at least one antidepressant.

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Received Jan. 3, 2007; accepted March 26, 2007. *From Finney Psychotherapy Associates, Norfolk, Va. (Dr. Truman); the Affective Disorders Program, Silver Hill Hospital, New Canaan, Conn., and the Department of Psychiatry, Mount Sinai School of Medicine, New York N.Y. (Dr. Goldberg); the Department of Psychiatry and Behavioral Sciences, Bipolar Disorder Research Program, Emory University, Atlanta, Ga. (Dr. Ghaemi); the Department of Psychiatry, the University of Pennsylvania, Philadelphia (Drs. Baldassano and Thase); University of Pittsburgh Medical Center and the Western Psychiatric Institute and Clinic, Pittsburgh, Pa. (Drs. Wisniewski and Thase); the Department of Psychological Sciences, Purdue University, West Lafayette, Ind. (Dr. Dennehy); and the Department of Psychiatry, Partners Bipolar Treatment Center, Massachusetts General Hospital, Harvard Medical School, Boston (Dr. Sachs).*

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Corresponding author and reprints: Joseph F. Goldberg, M.D., Silver Hill Hospital, 208 Valley Rd., New Canaan, CT 06840 (e-mail: JFGoldberg@yahoo.com).

Depression remains the most common and disabling phase of illness associated with bipolar disorder.[1,2] Traditional antidepressant agents are widely used for the treatment of bipolar depression despite a limited database to support their efficacy and safety.[3] Notably, the phenomenon of abnormal mood elevation during antidepressant treatment has been recognized to occur in about 15% to 20% of individuals with bipolar disorder,[4] although limited information exists to identify risk factors for such outcomes. The present study examined the historical presence and illness correlates of antidepressant-associated mania or hypomania among the first 500 subjects enrolling in the National Institute of Mental Health (NIMH) Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).

Previous reports suggest that treatment-emergent affective switch may be more common in bipolar patients with a previous history of antidepressant-induced mania, bipolar I (versus II) disorder,[5] comorbid substance

TAKE-HOME POINTS

- Antidepressants are associated with the potential risk for treatment-emergent mania or hypomania in patients with bipolar disorder.
- Bipolar patients with a short duration of illness, multiple antidepressant trials, and past experience of switch with at least 1 antidepressant may be at particularly high risk.
- Clinicians should make every effort to clarify patient-specific vulnerabilities when considering risk-benefit ratios for the treatment of bipolar depression.

abuse,[6,7] recent mania/hypomania,[8] hyperthymic temperament,[9] younger age or earlier illness onset,[6,10,11] or a genetic risk based on a polymorphism of the serotonin transporter gene.[12] Prior literature further suggests an inherently greater risk for treatment-emergent mania with the use of certain antidepressants, such as venlafaxine[13] or tricyclic antidepressants,[14] although such studies have not considered patient-specific baseline factors potentially contributing to an intrinsic vulnerability for affective polarity switch after antidepressant exposure.

A recent meta-analysis concluded that antidepressants pose no greater risk than placebo for inducing mania in bipolar depression[15]; however, inclusion of a disproportionate number of subjects in that meta-analysis from a single randomized trial, in which olanzapine added to fluoxetine was construed as "placebo" added to fluoxetine, limits the extent to which generalizations can be drawn about the potential safety of antidepressants. Two observational studies of 1-year antidepressant outcomes after acute treatment for bipolar depression found high rates of depression relapse with antidepressant cessation but rare switches to mania during long-term antidepressant continuation.[16,17] While these findings would seem provocative, causal inferences about the effects of antidepressant continuation or cessation cannot be drawn from these studies because of their noncontrolled designs—that is, subjects may have relapsed following antidepressant cessation or simply may have stopped taking antidepressants after relapsing. Moreover, antidepressant continuation was feasible for only a small minority of acutely depressed bipolar patients (~15%) in the outcome study by Altshuler and colleagues,[16] which also excluded patients with DSM-IV rapid cycling.

While randomized, controlled trials represent an ideal strategy to resolve uncertainties about the safety of antidepressants, traditional efficacy-based studies often exclude "real-world" patients for whom factors such as comorbid substance abuse[6,7] could influence switch rates with antidepressants. Because observational (or effectiveness) studies impose fewer exclusionary criteria for subject enrollment, they provide greater opportunity to identify moderators and mediators of outcome that may be altogether absent in samples recruited for traditional efficacy trials. Most existing observational studies either have not attempted to control for such factors in multivariate models or else have involved sample sizes that lacked adequate power to identify potential confounding variables.[7]

The present investigation utilized data from a large, nationwide effectiveness study of bipolar disorder in order to (a) compare risks for affective polarity switch among various antidepressant classes in a large, well-characterized bipolar cohort and (b) identify clinical features associated with manic/hypomanic switch utilizing multiple regression analyses to control for potential confounding factors.

METHOD

The study cohort included the first 500 patients enrolled in STEP-BD, a multi-site, NIMH-funded project that includes a large prospective, naturalistic study and a series of randomized, controlled trials. All participants received the same standardized assessments at baseline and during subsequent treatment visits, as well as quarterly outcome assessments. Full study procedures, outcome measures, and sample characteristics have been described in detail elsewhere.[18,19] The protocol was approved by the institutional review board at each site, and all participants provided oral and written consent.

Study Participants and Procedures

STEP-BD subjects in the present study were enrolled in the protocol between November 1999 and November 2000. Subjects were required to be at least 15 years of age and to be able to give informed consent. For participants aged 15 to 17 years, written assent was obtained along with written consent from a parent or legal guardian. All bipolar subtypes (bipolar I, bipolar II, bipolar not otherwise specified, or cyclothymia) were included, as well as patients with schizoaffective bipolar disorder.

Diagnoses were made from screening interview batteries conducted by experienced clinical investigators who underwent certification training in the administration of study diagnostic instruments. These included (1) the Mini-International Neuropsychiatric Interview (MINI)[20] and (2) a standardized Affective Disorder Evaluation (ADE),[18] which integrates mood and psy-

Table 1. Clinical Characteristics of Subjects With or Without Antidepressant-Associated Manic/Hypomanic Switch

Characteristic	Full Antidepressant-Exposed Sample (N = 338)	No History of Switch (N = 188)	History of Switch (N = 150)	Test Statistic	df	p
Age, mean ± SD, y	42.13 ± 12.9	44.02 ± 13.3	40.87 ± 12.2	t = 2.20	322	.029
Age at onset of illness, mean ± SD, y	15.12 ± 9.9	16.55 ± 9.3	15.20 ± 9.4	t = 1.31	336	.191
Duration of illness, mean ± SD, y	26.87 ± 14.5	27.37 ± 14.2	25.52 ± 13.8	t = 1.19	322	.234
Marital status, % (N)[a,b]						
Never married	35.5 (108)	32.2 (55)	39.8 (53)	$\chi^2 = 1.93$	2	.38
Married	40.1 (122)	42.1 (72)	37.6 (50)			
Separated/divorced	24.3 (74)	25.7 (44)	22.6 (30)			
Race/ethnicity, % (N)[c]						
White/Caucasian	93.4 (311)	94.1 (175)	92.5 (136)	$\chi^2 = 0.328$	1	.567
Other	6.6 (22)	5.9 (11)	7.5 (11)			

[a]Because of incomplete data availability, percentages are based on N = 304 (full antidepressant-exposed sample), N = 171 (no history of switch), and N = 133 (history of switch).
[b]Percentage total (full antidepressant-exposed sample) is less than 100 because of rounding.
[c]Because of incomplete data availability, percentages are based on N = 333 (full antidepressant-exposed sample), N = 186 (no history of switch), and N = 147 (history of switch).
Abbreviation: OR = odds ratio.

chosis modules from the Structured Clinical Interview for DSM-IV diagnosis (SCID).[21] The ADE also obtained information about illness onset, prior episodes, past treatment and response, childhood psychopathology, comorbid medical and psychiatric conditions, psychoactive substance use, and family history.

The ADE treatment history module records yes/no responses to direct queries regarding exposure to more than 30 standard treatment options for the treatment of bipolar disorders, including mood stabilizing agents, electroconvulsive therapy (ECT), antidepressant and antipsychotic medications, as well as light treatment and psychotherapy. The ADE records prestudy treatment exposures using a yes/no format; therefore, multiple trials of the same antidepressant medication are recorded as a single entry. As a result, each antidepressant trial described in this analysis represents *at least one* trial of a given treatment. STEP-BD defined *manic/hypomanic switch* as a report of mania, hypomania, or a mixed episode within the first 12 weeks of a given treatment. The retrospective assessment design did not permit finer distinctions between antidepressant-associated manias and hypomanias by DSM-IV criteria, and either outcome was counted as a switch event. Histories of manic/hypomanic switches were ascertained by direct subject report at the baseline interview and recorded as a yes/no response for each treatment queried.

Statistical Analysis

For baseline characteristics, t tests were used to test for differences in the means of all continuous variables such as age, length of illness, and age at onset of illness. For categorical variables, such as gender, race, and employment, either χ^2 or Fisher exact probability tests were used, as appropriate. All statistical tests were 2-tailed with an α level of .05. Alpha levels were not corrected for multiple comparisons, because univariate analyses were conducted in exploratory fashion to screen candidate variables for entry into a subsequent multivariate regression model.

Predictors of polarity switch were examined using SAS software (v. 8.2; SAS Institute, Cary, N.C.) with stepwise logistic regression analyses using odds ratios (ORs) and 95% CIs. All models were adjusted for duration of illness, including all interim models in the stepwise selection process. In order to assess the hazards associated with individual antidepressants, we used generalized estimating equations. This approach permitted within-subject correlations to be controlled, as many subjects had been treated with multiple antidepressants. In assessing manic switch for different antidepressant classes, selective serotonin reuptake inhibitors (SSRIs), heterocyclics, and monoamine oxidase inhibitors (MAOIs) were grouped separately.

RESULTS

Of the first 500 entrants into STEP-BD, 395 reported at least one prior trial of antidepressant medication prior to study entry. Complete data regarding a history of manic switch were available for 338 subjects. The 57 subjects with incomplete data were excluded from the present study.

Within the final cohort of 338 STEP-BD participants with at least one antidepressant trial and complete data on switch history, 150 (44.4%) reported histories of at least one manic switch. A comparison of clinical and demographic characteristics of those subjects with and without a history of polarity switch is presented in Tables 1 and 2. Those with a history of antidepressant-associated manic switch were significantly younger, had a history of lifetime rapid cycling, and were more likely to report exposure to multiple antidepressant medications than those without such a history. Gender, family history of bipolar

Table 2. Clinical Features of Bipolar Patients With and Without Antidepressant-Associated Manic/Hypomanic Switch

Clinical feature	Total Sample (N = 338[a]), % (N)	No History of Switch (N = 188[a]), % (N)	History of Switch (N = 150[a]), % (N)	Test Statistic	df	p Value	OR (95% CI)
Sex							
Male	38.0 (128)	37.4 (70)	38.7 (58)	$\chi^2 = 0.054$	1	.817	1.05 (0.68 to 1.64)
Female	62.0 (209)	62.6 (117)	61.3 (92)				
Bipolar subtype							
I	71.6 (242)	74.5 (140)	68.0 (102)	FET = 1.820	2	.395	0.71 (0.43 to 1.17)
II	25.1 (85)	22.3 (42)	28.7 (43)				
Other	3.3 (11)	3.2 (6)	3.3 (5)				
History of past-year rapid cycling	21.2 (69)	17.0 (31)	26.6 (38)	$\chi^2 = 4.36$	1	.037	1.76 (1.03 to 3.01)
No history of past-year rapid cycling	78.8 (256)	83.0 (151)	73.4 (105)				
Family history of bipolar illness	91.0 (303)	56 (169)	44 (134)	$\chi^2 = 0.066$	1	.794	0.91 (0.43 to 1.92)
No family history of bipolar illness	9.0 (30)	53 (16)	47 (14)				
History of substance abuse or dependence	41.8 (135)	53 (71)	47 (64)	$\chi^2 = 0.593$	1	.441	1.19 (0.76 to 1.86)
No history of substance abuse or dependence	58.2 (188)	57 (107)	43 (81)				
Prior manic phases, No.							
≤ 2	12.7 (41)	58 (23)	44 (17)	$\chi^2 = 5.41$	8	.248	…
3–4	18.0 (58)	57 (33)	43 (25)				
5–9	19.3 (62)	68 (42)	32 (20)				
10–20	15.8 (51)	50 (25)	50 (25)				
> 20	34.2 (110)	51 (56)	49 (54)				
Prior treatment with mood stabilizer	87.0 (294)	55 (161)	45 (133)	$\chi^2 = 0.676$	1	.411	1.31 (0.69 to 2.51)
No prior treatment with mood stabilizer	13.0 (44)	61 (27)	39 (17)				
	Mean (SD)	Mean (SD)	Mean (SD)				
Antidepressant trials, No.	3.05 (2.0)	2.63 (1.8)	3.58 (2.0)	t = –4.47	338	< .0001	…
Patients reporting a trial of	% (N)	% (N)	% (N)				
1 antidepressant	25.1 (85)	71 (60)	29 (25)	$\chi^2 = 31.78$	3	< .0001	…
2 antidepressants	24.6 (83)	71 (59)	29 (24)				
3–4 antidepressants	29.3 (99)	38 (38)	62 (61)				
≥ 5 antidepressants	21.0 (71)	44 (31)	56 (40)				

[a]Variability in column numbers reflects missing data for variable being examined.
Abbreviations: FET = Fisher exact test, OR = odds ratio.
Symbol: … = odds ratios not calculable for continuous variables.

illness, bipolar subtype, history of substance abuse or dependence, and number of prior manic episodes were not significant correlates of antidepressant-associated switch to mania/hypomania.

The mean ± SD number of exposures to antidepressants was significantly higher in patients with a history of polarity switch than those without such a history (3.64 ± 2.1 vs. 2.63 ± 1.8 trials, p = .001). Among the 150 subjects reporting a history of manic switch, 54 (36.0%) reported affective switches with 2 or more different antidepressant medications, and 24 (15.0%) reported affective switches with 3 or more different antidepressant medications.

In a stepwise logistic regression model, 2 predictors of manic/hypomanic switch emerged as significant predictors of antidepressant-associated switch: shorter duration of illness (OR = 1.02, 95% CI = 1.01 to 1.04) and a history of multiple antidepressant trials (OR = 1.73, 95% CI = 1.38 to 2.16). While lifetime history of rapid cycling was a significant correlate of antidepressant-associated switch in univariate analyses, this variable was no longer significant when controlling for other parameters in the model.

Reports of manic/hypomanic switch with different antidepressants are summarized in Table 3. Subjects were half as likely to report manic switches during MAOI treatment (OR = 0.16, 95% CI = 0.08 to 0.36) as compared to all other antidepressant classes. These observations remained significant after controlling for duration of illness and a history of rapid cycling. No other single treatment or class (ECT, SSRIs, mirtazapine, bupropion, venlafaxine, nefazodone, and heterocyclics) was found to have a significant association with manic/hypomanic switch when compared to all other treatments.

As shown in Table 4, if patients had switched with any other antidepressant medications, they were also more likely to switch with tricyclic antidepressants, SSRIs (with the exception of fluvoxamine), or bupropion. Those patients who switched to mania/hypomania during treatment with one of those agents on a separate occasion had a 2- to 5-fold increased risk for a subsequent mania or hypomania switch with any antidepressant. However, among individual SSRIs, fluoxetine was associated with an approximately 2.7-fold increased risk for switch to mania/hypomania, while nefazodone had a significantly lower rate of polarity switches as compared to all other treatments.

Table 3. Study Subjects Reporting At Least 1 Antidepressant Trial and Presence or Absence of Antidepressant-Associated Manic/Hypomanic Switch

Intervention	Patients Reporting Trials Without Manic/Hypomanic Switch, % (N)	Patients Reporting Trials With Manic/Hypomanic Switch, % (N)	OR[a]	95% Confidence Interval
Heterocyclics	77 (61)	23 (18)	1.18	0.68 to 2.04
MAOIs	87 (130)	13 (6)	0.16	0.07 to 0.36
ECT	85 (41)	15 (7)	0.66	0.29 to 1.49
1 or more SSRI trials[b]	67 (230)	33 (113)	3.13	2.27 to 4.30
Citalopram	83 (53)	17 (11)	0.95	0.41 to 1.57
Fluoxetine	68 (145)	32 (69)	2.69	1.93 to 3.74
Sertraline	81 (150)	19 (35)	1.09	0.73 to 1.62
Paroxetine	84 (144)	16 (28)	0.88	0.57 to 1.36
Fluvoxamine	88 (30)	12 (4)	0.61	0.21 to 1.74
Bupropion	83 (163)	17 (33)	0.76	0.50 to 1.14
Mirtazapine	91 (30)	9 (3)	0.39	0.12 to 1.27
Nefazodone	93 (56)	7 (4)	0.27	0.10 to 1.74
Venlafaxine	82 (79)	18 (17)	0.83	0.48 to 1.44

[a]OR reflects probability of a switch event's occurring with a given agent relative to all others.
[b]Analysis for SSRIs as a class compared to other antidepressants did not include the separate specific SSRI trials. In contrast, analysis for each specific SSRI included the separate specific SSRI trials added to all other antidepressants.
Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, OR = odds ratio, SSRI = selective serotonin reuptake inhibitor.

Table 4. Probability of Manic Switch Based on History of Manic/Hypomanic Switch With Another Antidepressant[a]

Manic/Hypomanic Switch Associated With:		Manic Switch Associated With Another Antidepressant				
		No	Yes	χ^2	p	OR (95%CI)
TCAs		N = 28	N = 32	7.69	.005	7.80 (1.56 to 28.9)
	% Switched	7.1	37.5			
MAOIs		N = 21	N = 13	0.008	.930	1.09 (0.16 to 7.59)
	% Switched	14.3	15.4			
ECT		N = 22	N = 14	1.22	.270	2.53 (0.47 to 13.6)
	% Switched	13.6	28.6			
≥ 1 SSRIs		N = 136	N = 61	17.45	< .0001	3.73 (1.98 to 7.05)
	% Switched	26.5	57.4			
Citalopram		N = 26	N = 17	9.46	.0002	17.5 (1.90 to 161.4)
	% Switched	3.8	41.2			
Fluoxetine		N = 102	N = 61	14.58	.0001	3.63 (1.85 to 7.14)
	% Switched	24.5	54.1			
Sertraline		N = 68	N = 63	7.24	.007	3.11 (1.33 to 7.27)
	% Switched	14.7	34.9			
Paroxetine		N = 65	N = 62	16.77	< .0001	8.39 (2.69 to 26.2)
	% Switched	6.2	35.5			
Fluvoxamine		N = 12	N = 12	0.381	.537	2.20 (0.17 to 28.1)
	% Switched	8.3	16.7			
Bupropion		N = 80	N = 59	10.70	.0011	4.28 (1.72 to 10.6)
	% Switched	10	32.2			
Mirtazapine		N = 8	N = 10	0.180	.671	1.75 (0.13 to 23.7)
	% Switched	12.5	20.0			
Nefazodone		N = 16	N = 24	2.96	.085	< 3.20 (0.32 to 31.5)
	% Switched	0	16.7			
Venlafaxine		N = 34	N = 35	0.592	.442	1.54 (0.51 to 4.67)
	% Switched	20.6	28.6			

[a]Varying Ns reflect number of subjects who received each treatment.
Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

DISCUSSION

The present retrospective study represents the largest investigation of affective polarity switch during treatment with contemporary antidepressants for bipolar disorder. The observed lifetime prevalence of 44% is comparable to similar rates reported by Goldberg and Whiteside[6] (42%) and Ghaemi et al.[22] (49%) but higher than those reported by Altshuler et al.[16] (35%), Boerlin et al.[11] (28%), Henry et al.[9] (27%), or Joffe et al.[17] (16%). Methodological variations across studies may account for differences in reported prevalence rates of antidepressant-induced mania, including factors such as small sample sizes, retrospective recall, diversity of specific antidepressants and

mood stabilizers, inconsistencies of medication dosing and adherence, failure to control for potential confounding factors,[7] and variation in the operational definition of *manic switch*. While the present findings are limited by the retrospective and nonrandomized study design, the use of regression modeling to control for potential confounding factors provides an advantage relative to most existing reports in this area.

A key aspect of the current findings, particularly in relation to prior reports, is the observation that past antidepressant-associated manic switches pose a risk for additional switch events with other antidepressants. This observation is consistent with observations of a *patient-specific vulnerability* to antidepressant-induced mania identified in several prior reports[6,7,12,23] but contrasts with findings from the Stanley Bipolar Network,[24] where such an association was not seen during prospective 10-week acute treatment with bupropion, sertraline, or venlafaxine added to mood stabilizers. The extent to which antidepressant-associated mania reflects an adverse iatrogenic event (as conceptualized within DSM-IV) or an evoked response within a subgroup of vulnerable individuals with bipolar disorder (as formulated in DSM-III-R) remains a critical, unresolved issue. It is possible that antidepressant-associated switches arise as the confluence of patient-specific and medication-specific factors in a diathesis-stress model for a subgroup of individuals with bipolar disorder. It is conceivable that the relative risk for switch events with specific antidepressants also may differ in patients once they have been sensitized to antidepressants, or had prior switches. Studies that report relatively high rates of lifetime manic switch (e.g., Ghaemi et al.[22]), including the present one, may also reflect an enriched sample of tertiary care patients from academic settings for whom this baseline diathesis may be especially high. However, the STEP-BD purposefully employed broad inclusion criteria in an effort to enroll patients who were representative of individuals with bipolar disorder from across the United States. Patients were not selected for treatment resistance or atypical demographic features.

Significant predictors of manic switch for the current study group included younger age and greater past exposure to antidepressants. These findings were independent of age at onset of illness and may suggest a vulnerable period early in the course of bipolar illness. Among the more commonly used antidepressants, rates of manic/hypomanic switch were relatively similar across SSRIs, bupropion, and venlafaxine. MAOIs were associated with lower reported rates of manic/hypomanic switch than other classes. Patients were more likely to report a history of manic/hypomanic switch with bupropion, citalopram, fluoxetine, sertraline, paroxetine, or tricyclic antidepressants if they also had a history of switch with at least 1 other antidepressant agent.

The lower reported manic/hypomanic switch rate with MAOIs seen in the present study contrasts with findings from a previous randomized trial by Himmelhoch and colleagues,[25] which found no difference in switches between tranylcypromine or imipramine (N = 56); however, patients in that latter study were not routinely taking adjunctive mood stabilizers. Another nonrandomized study[11] found comparable switch rates between tricyclic antidepressants and MAOIs, both of which were higher than seen with fluoxetine, although the small sample size (N = 29) and lack of control for potential confounding factors limit generalizability of the findings. In addition, Bottlender and colleagues[26] reported lower rates of switches to mania during treatment for bipolar depression with an MAOI (regardless of the presence of a concomitant mood stabilizer) relative to switch rates seen with tricyclic antidepressants.

It was also notable that all SSRIs were not equal in their associations with treatment-emergent mania/hypomania, since the overall class risk was elevated, driven predominantly by fluoxetine. These results are consistent with the only randomized study of fluoxetine alone in bipolar I disorder,[27] in which a 16% manic switch rate was noted during crossover treatment with fluoxetine, a rate similar to that of imipramine. Manic switch risk may be lower with coadministration of olanzapine[28] or in bipolar II disorder.[29] These data suggest that, in real-world practice, fluoxetine may carry higher risk than other SSRIs.

The main limitations of the present study, similar to other observational studies, involve its noncontrolled, nonrandomized design and retrospective assessment of historical switch events. Information about past antidepressant doses, concomitant mood stabilizer treatments, pharmacotherapy adherence, and fulfillment of DSM-IV criteria for past mania or hypomania were not systematically available. The retrospective design also may have limited the accuracy with which the historical count of lifetime antidepressant trials could be recorded. The observed relationship between antidepressant-induced mania and short duration of illness could also have been influenced by recall bias or possibly more extensive treatment with mood stabilizing agents later in the course of illness. Cell sizes for some specific antidepressant trials in the current study group were relatively low (e.g., mirtazapine), limiting the statistical power with which to detect possible differences. Hence, outcomes with specific antidepressant agents must be interpreted with caution and may serve more to generate rather than test hypotheses for affirmation in controlled trials.

In summary, antidepressant-associated mania appears evident across a range of antidepressant classes and may be influenced by patient-specific vulnerability factors. Identifying and controlling for such potential factors and their interplay with specific antidepressants and adjunc-

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tive mood stabilizers represents a critical next step for clarifying risk-benefit ratios when using antidepressants for bipolar depression.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, bupropion, citalopram, fluoxetine, imipramine, mirtazapine, olanzapine, paroxetine, sertraline, venlafaxine, fluvoxamine, and nefazodone are not approved by the U.S. Food and Drug Administration for the treatment of bipolar depression. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

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STEP-BD Sites and Principal Investigators: Baylor College of Medicine (Lauren B. Marangell, M.D.); Case University (Joseph R. Calabrese, M.D.); Massachusetts General Hospital and Harvard Medical School (Andrew A. Nierenberg, M.D.); Portland VA Medical Center (Peter Hauser, M.D.); Stanford University School of Medicine (Terence A. Ketter, M.D.); University of Colorado Health Sciences Center (Marshall Thomas, M.D.); University of Massachusetts Medical Center (Jayendra Patel, M.D.); University of Oklahoma College of Medicine (Mark D. Fossey, M.D.); University of Pennsylvania Medical Center (Laszlo Gyulai, M.D.); University of Pittsburgh Western Psychiatric Institute and Clinic (Michael E. Thase, M.D.); University of Texas Health Science Center at San Antonio (Charles L. Bowden, M.D.).

Additional details on STEP-BD can be located at http://www.stepbd.org.

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