The Association Between Substance Abuse and Antidepressant-Induced Mania in Bipolar Disorder: A Preliminary Study

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Background: Estimates of the prevalence and features of antidepressant-induced mania vary widely, with few data available on its potential risk factors.

Method: Fifty-three DSM-IV bipolar patients were interviewed to retrospectively identify lifetime affective episodes, pharmacotherapy trials, and clinical outcomes, with corroboration from treating clinicians and reviews of medical, psychiatric, and pharmacy records. Particular attention was given to the possible relationship between antidepressant-induced mania and the presence of psychoactive substance abuse or dependence.

Results: Antidepressant-induced mania or hypomania was evident in 39.6% (21/53) of the study group. Patients who developed manic features soon after starting an antidepressant had more antidepressant trials per year than those who did not ($p < .05$). A history of substance abuse and/or dependence was associated with substantially increased risk for antidepressant-induced mania (odds ratio = 6.99, 95% CI = 1.57 to 32.28, $p = .007$). Concomitant mood stabilizers were not uniformly associated with protection against inductions of mania during antidepressant trials.

Conclusion: Multiple antidepressant exposures among bipolar patients with histories of substance abuse and/or dependence may be associated with an elevated risk for antidepressant-induced mania.

(J Clin Psychiatry 2002;63:791–795)

Received Dec. 10, 2001; accepted May 3, 2002. From the Department of Psychiatry, Weill Medical College of Cornell University (Dr. Goldberg); and the Bipolar Disorders Research Clinic, New York Presbyterian Hospital-Payne Whitney Clinic (Drs. Goldberg and Whiteside), New York, N.Y.

Supported by research grants from the Theodore and Vada Stanley Foundation, a NARSAD Young Investigator Award, the Alcoholic Beverage Medical Research Foundation, the Nancy Pritzker Foundation, and by resources from a fund established in the New York Community Trust by DeWitt Wallace (Dr. Goldberg).

Presented in part at the 154th annual meeting of the American Psychiatric Association, May 5–10, 2001, New Orleans, La.

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Dr. Goldberg is a consultant for Lilly, AstraZeneca, Novartis, GlaxoSmithKline, Abbott, and Janssen; has received research grant support from Lilly, AstraZeneca, Novartis, GlaxoSmithKline, Abbott, Janssen, Robert Wood Johnson, Shire, Britol-Myers, Forest, and Cyberonics; and has received honoraria from and is a member of the speakers/advisory board for Lilly, Novartis, Abbott, Janssen, and GlaxoSmithKline. Dr. Whiteside has no significant commercial relationship to disclose relative to the presentation.

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Antidepressant-induced mania has been described in 30% to 70% of bipolar patients but remains a source of enormous controversy.[1] Little is known about which bipolar patients, and at which timepoints in their illness course, are most susceptible to its occurrence. Some authors therefore advocate the minimal use of antidepressants, for short exposures, in bipolar patients unresponsive to mood stabilizers alone.[2] Others question this stringency, citing high suicide rates in bipolar depression, a discernible risk for depression relapse off treatment with antidepressants,[3] and the paucity of empirical information on pro-cycling risks versus antidepressant benefits.[4]

Prior studies suggest that antidepressant-induced manias may be of milder intensity and shorter duration than spontaneous manias.[5,6] The phenomenon may be more common with tricyclics than selective serotonin reuptake inhibitors (SSRIs),[7] although few contemporary data exist to affirm this distinction, which some authors have questioned.[8] Concurrent mood stabilizers (e.g., lithium, valproate) may not routinely prevent SSRI-induced manias[9,10] and may not always confer protection against inductions by tricyclics.[11] Antidepressant-induced manias have been reported during cotherapy with valproate, even with serum valproate levels within the standard thera-

peutic range, although switches may be more likely to occur at lower than at higher serum levels.[12] Furthermore, robust clinical correlates or predictors of antidepressant-induced mania have not been identified,[13] although recent candidate gene polymorphism studies suggest a possible genetic determinant to this phenomenon involving a short allelic variant of the promoter region of the serotonin transporter gene.[14]

We hypothesized that antidepressants may be more likely to destabilize mood in bipolar patients for whom other forms of central nervous system (CNS) excitation occur, notably, by psychoactive substance abuse or dependence. Conceivably, both substance misuse and antidepressant-induced mania could reflect mechanisms related to behavioral sensitization or kindling in a subgroup of bipolar patients.[15]

METHOD

Study Subjects

Subjects were 53 bipolar outpatients (33 bipolar I, 18 bipolar II, and 2 bipolar not otherwise specified) consecutively evaluated for treatment in the Bipolar Disorders Research Clinic of the New York Presbyterian Hospital (New York, N.Y.). All were diagnosed by the authors using the Structured Clinical Interview for DSM-IV-Clinician Version (SCID).[16] Lifetime affective episodes were retrospectively rated using the Life Chart Method[17] administered by the authors during comprehensive baseline evaluations. Lifetime trials of antidepressants and mood stabilizers (lithium, divalproex sodium, carbamazepine) were rated for dosing, duration, and clinical outcome. Data were corroborated for all subjects by review of psychiatric, hospital, and/or pharmacy records, as well as interviews with family members and past or current treating clinicians. The authors consensus-rated probable or definite manic or hypomanic symptom constellations by DSM-IV criteria for the 12-week period after starting each antidepressant. Subjects were included for study only when histories from pooled sources could be rated with reasonable confidence.

All subjects provided written informed consent to participate in the study protocol, which was approved by the Institutional Review Board of the Weill Medical College of Cornell University (New York, N.Y.).

Statistical Methods

Dichotomous variables were analyzed with chi-square or Fisher exact tests. Mean group differences in continuous variables were compared with Mann-Whitney tests. Odds ratios (ORs) with 95% CIs were calculated using StatXact software.[18] All statistical tests were 2-tailed. To adjust for multiple comparisons, a Bonferroni-corrected alpha of .006 (.05/8) was applied to the data reported in Table 1.

Table 1. Characteristics of Bipolar Patients With or Without Histories of Antidepressant-Induced Mania or Hypomania[a]

Variable	History of Antidepressant-Induced Mania: Present	Absent	p Value
Female	12/21 (57.1)	19/32 (59.4)	1.000[b]
Age at illness onset, mean (SD), y	20.7 (11.9)	18.1 (8.8)	.532[c]
Comorbid substance abuse or dependence	12/20 (60.0)	5/28 (17.8)	.005[b]
Depressed polarity at first episode	19/20 (95.0)	22/27 (81.4)	.221[b]
Bipolar II	8/19 (42.1)	10/25 (40.0)	.887[d]
Antidepressant trials/year,[e] mean (SD)	0.20 (0.14)	0.12 (0.10)	.041[c]
Bipolar family history	10/18 (56)	10/22 (46)	.525[f]

[a]Values shown as N/total N (%) unless noted otherwise.
[b]Fisher exact test.
[c]Mann-Whitney test.
[d]$\chi^2 = 0.02$, df = 1.
[e]Based on complete data for 19 of 21 patients with inductions and 28 of 32 without inductions.
[f]$\chi^2 = 0.40$, df = 1.

RESULTS

The study group had a mean (SD) age of 43.5 (13.6) years; 58.5% (31/53) were female, and 86.8% (46/53) were white. Subjects had a mean (SD) lifetime illness duration of 24.4 (10.7) years. Rapid cycling by DSM-IV criteria was present in 26.1% (12/46 evaluable subjects), while 35.4% (17/48 evaluable subjects) had lifetime histories of psychoactive substance abuse or dependence identified with the SCID.

A history of at least 1 episode of antidepressant-induced mania or hypomania was evident in 21 (39.6%) of the 53 study subjects; 17 (81.0%) of 21 had only 1 switch, 3 (14.3%) had 2 lifetime switch episodes, while 1 (4.8%) had ≥ 3 such episodes. For the total sample (N = 53), 164 individual antidepressant trials occurred, from which 26 (15.9%) resulted in a manic or hypomanic switch. The mean (SD) time from antidepressant initiation to induction of mania was 36.4 (33.2) days. Data on outcomes of switch events were available for 19 subjects. The most frequent outcomes included (1) cessation of antidepressant alone (N = 10; 52.6%), (2) no intervention (N = 5; 26.3%), (3) antidepressant cessation plus addition or change in mood stabilizer (N = 3; 15.8%), and (4) antidepressant continuation with mood stabilizer addition (N = 1; 5.3%).

Clinical features of subjects with or without histories of antidepressant-induced mania or hypomania are presented in Table 1. (Sample sizes vary on the basis of the availability of complete data, as noted.) Inductions of mania or hypomania were associated with a significantly greater lifetime number of antidepressant trials. In addition, antidepressant-induced mania or hypomania was strongly associated with a history of substance abuse/dependence (OR = 6.99, 95% CI = 1.57 to 32.28;

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Table 2. Doses of Antidepressants and Mood Stabilizers for Subjects With Antidepressant-Induced Mania or Hypomania[a]

Subject[b]	Antidepressant	Dose at Switch, mg/d	Taking Divalproex, Carbamazepine, or Lithium?
1 (WM, 22 y)	Venlafaxine	Unknown	No
2 (WF, 15 y)	Bupropion	300	No
3 (WF, 26 y)	Bupropion	75	No
4 (BM, 33 y)	Fluoxetine	40	No
5 (HF, 55 y)	Imipramine	Unknown	No
6 (HM, 58 y)	Imipramine	75	No
7 (WF, 44 y)	Fluoxetine	20	No
8 (WF, 49 y)	Paroxetine	10	No
9 (WM, 46 y)	Imipramine	75	No
10 (HF, 30 y)	Fluoxetine	50	Divalproex (dose unknown)
11 (HM, 53 y)	Bupropion	225	Lithium, 900 mg/d
12 (WM, 31 y)	Fluoxetine	40	No
(42 y)	Citalopram	40	Divalproex, 1500 mg/d
13 (WM, 51 y)	Nefazodone	600	Lithium, 900 mg/d
14 (WM, 34 y)	Paroxetine	40	Lithium, 1200 mg/d
15 (WF, 39 y)	Sertraline	100	No
(40 y)	Bupropion	100	No
(40 y)	Venlafaxine	112.5	No
16 (WF, 46 y)	Paroxetine	20	Lithium, 900 mg/d
17 (WF, 61 y)	SAMe	400	No
18 (WF, 31 y)	Fluoxetine	20	Divalproex, 1250 mg/d
(29 y)	Sertraline	50	Divalproex, 1250 mg/d
19 (HF, 27 y)	Fluvoxamine	50	Divalproex, 1250 mg/d
20 (WM, 31 y)	Bupropion	300	No
(31 y)	Venlafaxine	300	No
21 (WF, 28 y)	Venlafaxine	150	Divalproex, 1500 mg/d

[a]Abbreviations: B = black, F = female, H = Hispanic, M = male, SAMe = *S*-adenosylmethionine, W = white.
[b]Ages shown as age at time of switch event; subjects 12, 15, 18, and 20 experienced multiple episodes of antidepressant-induced mania or hypomania.

p = .007). Among the 17 subjects with substance abuse/dependence, alcohol (with or without cannabis) was the most frequent drug of abuse (82.4%; 14/17), followed by cocaine (with or without cannabis) (17.6%; 3/17). Substance abuse preceded the first antidepressant-induced mania or hypomania by >1 year in nearly all instances.

Of a total of 26 antidepressant trial switch events (among 21 patients who had switched), 12 (46.2%) were associated with SSRI use, 3 (11.5%) were associated with tricyclic use, 5 (19.2%) occurred with bupropion, 4 (15.4%) occurred with venlafaxine, and 2 (7.7%) occurred with other antidepressants (1 nefazodone, 1 *S*-adenosylmethionine). Data on antidepressant doses and corresponding use of divalproex, lithium, or carbamazepine at the time of switch events for each case are presented in Table 2.

Among a total of 72 SSRI trials, 12 (16.7%) were associated with an induction of mania, as were 3 (10.3%) of 29 tricyclic trials, 4 (25.0%) of 16 venlafaxine trials, 5 (20.0%) of 25 bupropion trials, and 2 (9.1%) of 22 trials of other antidepressants (nefazodone and *S*-adenosylmethionine) ($\chi^2 = 2.13$, df = 4, p = .71). Within the 164 individual antidepressant trials, documentation was available in 133 to affirm the concurrent use of a standard mood stabilizer (lithium, divalproex, carbamazepine; N = 81) or absence of a standard mood stabilizer (N = 52). Manic and hypomanic inductions occurred during 11 (13.6%) of 81 total antidepressant trials during which mood stabilizers were also administered and 9 (17.3%) of 52 total antidepressant trials without mood stabilizers ($\chi^2 = 0.344$, df = 1, p = .56).

To obtain provisional information about the relative protective role of lithium or anticonvulsant mood stabilizers with regard to antidepressant-induced manias or hypomanias, we compared switch rates stratifying by mood stabilizer group, both for the overall sample and for those with versus without histories of substance abuse/dependence. For the total sample, 75 antidepressant trials occurred while subjects were taking either (1) lithium with no divalproex or carbamazepine (N = 41) or (2) divalproex or carbamazepine (N = 34). Manic/hypomanic switches occurred in 4 (10%) of the 41 subjects taking lithium versus 6 (18%) of the 34 taking divalproex or carbamazepine (Fisher exact test, p = .50). For the 4 manic or hypomanic switches during lithium cotherapy, trough serum lithium levels exceeding 0.8 mEq/L could be confirmed in 2 cases. For the 6 switch events that occurred during valproate cotherapy, trough serum valproate levels exceeding 45 µg/mL could be confirmed in 4 of the 6 instances.

We separately compared antidepressant trial switch outcomes during lithium versus divalproex or carbamazepine coadministration for the subsample of subjects with substance abuse/dependence (N = 31 total trials) and for those without substance abuse/dependence (N = 15 total trials). For the subgroup with comorbid substance abuse/dependence, once again no significant differences were observed in switch event outcomes during trials with lithium coadministration (3 of 16 trials; 19%) versus divalproex or carbamazepine coadministration (6 of 15 trials; 40%) (Fisher exact test, p = .252). For subjects without histories of substance abuse/dependence, no switch event occurred while taking either lithium (N = 4) or divalproex/carbamazepine (N = 11).

DISCUSSION

The overall rate of antidepressant-induced mania and/or hypomania observed in this study (39.6% of subjects, or 16% of total individual antidepressant trials) is comparable to that reported among 51 bipolar patients described by Altshuler et al.[13] Antidepressant-related manic

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or hypomanic symptoms in the present group seldom led to hospitalization or marked functional impairment, consistent with observations by Stoll et al.,[5] but contrasting with more severe, psychotic manic symptoms induced by SSRIs as described by Howland.[8] Manias and hypomanias emerged during 10% to 25% of antidepressant trials across all major antidepressant classes without significant proportional differences. The potential 7-fold increased risk (by odds ratio) for antidepressant-induced mania we observed among bipolar patients with comorbid substance abuse suggests a significant vulnerability in this subpopulation; however, the precise magnitude of this risk cannot be fully estimated from the current findings due to the relatively wide confidence interval associated with the observed odds ratio.

Our finding that antidepressant-induced manias and hypomanias may be associated with multiple antidepressant trials and histories of substance abuse/dependence fits with other theoretical formulations that psychoactive excitation could destabilize mood in vulnerable bipolar populations. We have speculated that a causal pathway (psychoactive substance abuse, multiple antidepressant exposures) may predispose to eventual antidepressant-induced manias or hypomanias, although it is also possible that a subset of bipolar patients may exist with inherently greater mood instability, for whom multiple antidepressant trials may be undertaken and for whom substance abuse comorbidity may become merely a corollary of poor prognosis. However, the latter explanation may be less likely for the present findings insofar as substance abuse/dependence arose prior to antidepressant-induced manias in the vast majority of subjects.

If antidepressant-induced manias are in fact more likely to arise in a subset of bipolar patients especially vulnerable to environmentally sensitized mood destabilization, then the clinical risk assessments for this outcome might be improved by screening for other potential prosensitizing factors (e.g., psychoactive substance abuse, past manias resulting after circadian dysrhythmias such as sleep deprivation or travel across time zones). Further studies are needed to test the hypothesis that antidepressant-induced mania constitutes one of several manifestations of environmentally inducible mood destabilization in a discrete bipolar subgroup.

There is unresolved debate about whether lithium, divalproex, or other putative mood stabilizers reliably prevent evoked manias across antidepressant classes. Henry et al.[10] found a lesser likelihood of antidepressant-induced mania among bipolar patients taking lithium, but not among those taking an anticonvulsant mood stabilizer (divalproex). Stoner and colleagues[12] also found that 4 (44%) of 9 bipolar patients became manic when an antidepressant was added to valproate, even with serum valproate levels exceeding 50 μg/mL. The present findings showed a numerically higher proportion of switch outcomes for subjects taking an anticonvulsant mood stabilizer (divalproex or carbamazepine) than lithium. Although this difference was not statistically significant, it runs counter to the hypothesis that anticonvulsants might afford greater protection than lithium against mood destabilization when possible behavioral-sensitizing CNS events occur.

Nevertheless, the possibility remains that protection against iatrogenic mood switches may differ between lithium and anticonvulsants in bipolar subgroups for whom kindling events may be present. For example, lithium has been reported as less efficacious than anticonvulsant mood stabilizers after the passage of multiple episodes[19] or past exposures to significant substance abuse,[20] suggesting the possibility that antikindling drugs may confer greater protection against cyclicity or mood destabilization in the context of CNS-sensitizing events. The present findings would be consistent with the impact of substance abuse as such a prosensitizing event. However, in this preliminary, uncontrolled study, we did not observe differential protection against cycling with lithium versus anticonvulsant mood stabilizers in the relatively small subgroup of comorbid substance abuse patients for whom mood stabilizers were coadministered with antidepressants. The possibility cannot be ruled out that switch event outcomes could be influenced by differences in mood stabilizer dose optimization or longevity, antidepressant dose, or differential adherence to mood stabilizers.[21] In addition, whether CNS protective factors might exist that counterbalance the risk for environmentally induced mood destabilization also remains an area of speculation.

The present data did not reliably permit the finer-grained examination of manias versus hypomanias, or relationships between antidepressant dose-dependency and emergent mania and/or hypomania, particularly after initial favorable antidepressant responses. Complete data were also unavailable for all cases regarding medication adherence and blood levels of mood stabilizers, although based on narrative material from subject interviews and collateral history/record reviews, there was no impression of a systematic bias toward mood stabilizer nonadherence among subjects whose antidepressant trials did versus did not result in switch events. Moreover, the proportion of switch events that occurred during trials without mood stabilizer coadministration was found to be no higher than the rate of switch outcomes during trials with mood stabilizer coadministration.

It is presently unknown from empirical studies whether depressed bipolar patients who initially stabilize on treatment with an antidepressant medication remain susceptible to induced cycling after subsequent dose escalations or when and whether antidepressant dose reductions alone suffice to ameliorate such iatrogenic events, as has been suggested by at least 1 case report.[22] Relatedly, no convention exists for demarcating a time frame for

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most reliably attributing manias or hypomanias to recent antidepressant use, as opposed to the natural course of illness. Our observation that most manias or hypomanias arising shortly after antidepressant initiation occurred within the first 30 to 60 days would suggest that inductions beyond this time frame may be relatively rare.

Prospective, controlled studies with larger sample sizes are needed to affirm these preliminary observations suggesting a heightened risk for antidepressant-induced manias or hypomanias in bipolar patients with psychoactive substance abuse.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), citalopram (Celexa), divalproex sodium (Depakote), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, bupropion, citalopram, fluoxetine, fluvoxamine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of bipolar depression, and carbamazepine is not approved for the treatment of bipolar disorder.

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