Substance Use Disorder and Other Predictors of Antidepressant-Induced Mania: A Retrospective Chart Review

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Objective: To determine if substance use disorder (SUD) is a predictor of antidepressant-induced mania (ADM) in bipolar disorder, correcting for confounding factors in a regression model.

Method: 335 antidepressant trials were identified in 98 patients treated in an academic bipolar specialty clinic from 2000 to 2004. Patient charts were reviewed, and histories of SUD and ADM (primary outcome; defined as a hypomanic or manic episode within 12 weeks of beginning an antidepressant trial) were identified. Mood disorder diagnoses were made using the Structured Clinical Interview for DSM-IV mood module, and SUD diagnoses were defined using DSM-IV criteria. Potential confounding variables were also examined and included in a multivariable regression model. Concomitant mood stabilizer, antimanic, and antidepressant use was adjusted for in the regression model.

Results: In univariate analyses, there was no evidence of an association between ADM and past SUD. However, after adjustment for confounding variables in a multivariable regression model, there was a strong relationship (OR = 5.06, 95% CI = 1.31 to 19.64, $p < .05$). Other statistically significant predictors of ADM in the regression model were type II subtype of bipolar illness, female gender, and tricyclic antidepressant (TCA) use (vs. bupropion).

Conclusions: Along with other factors, a history of SUD was a strong predictor of ADM. Possible underestimation of ADM in randomized clinical trials may occur due to the exclusion of subjects with SUD. Type II illness, female gender, and TCA use also appeared to be predictors of ADM, while bupropion use appeared to predict lower likelihood of ADM.

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Antidepressant-induced mania (ADM), a manic, hypomanic, or mixed episode shortly following initiation of treatment with an antidepressant, is an important and controversial topic that complicates treatment for patients with bipolar disorder. Clinical experience suggests that antidepressants possess differential liability to such mania induction, with reported rates of 30% to 60% with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors,[1] compared to 10% to 20% with serotonin reuptake inhibitors (SRIs) or other new antidepressants.[2–7] While a recent meta-analysis of 5 placebo-controlled randomized clinical trials (RCTs) suggested that there was no association between antidepressant use and induction of mania,[8] there was marked heterogeneity between study designs in those RCTs: 2 studies did not use mood stabilizers,[9,10] 1 used olanzapine,[11] and 1 used lithium in an imbalanced manner between groups[12]; only 1 used lithium equally in all arms, and in that study there

was an elevated rate of acute mania with imipramine.[13] Regardless of whether or not the meta-analysis produced a valid result given that heterogeneity, it is important to examine why observational data find evidence of ADM, unlike many RCTs. Generalizability from RCTs may be relevant[14]: if risk factors for ADM are screened out of RCTs, one would predict underreporting of the risk of ADM.

Possible predictors of ADM implicated in at least one study include history of substance abuse, number of prior antidepressant treatments, type of antidepressant, concomitant use of mood stabilizers, age at onset of bipolar illness, severity of bipolar illness, rapid-cycling course, and family history of bipolar disorder.[15] However, studies are not consistent, which may reflect the fact that observational studies generally have not adjusted statistically for confounding bias (such as through multivariable regression modeling), as is standard practice in clinical epidemiology.[16]

One predictor of interest is substance abuse, since it is a routine cause for exclusion from RCTs investigating bipolar disorder. Some epidemiologic studies have shown a high rate of comorbidity between bipolar disorder and SUD. For example, the Epidemiologic Catchment Area study reported a 56.1% lifetime prevalence of SUD among people with bipolar disorder, higher than any other Axis I disorder.[17] The actual prevalence may be even higher, as bipolar disorder has been shown to be underdiagnosed among substance-abusing males.[18] The National Comorbidity Survey reports that among alcohol-dependent men, there is a 6.2% lifetime prevalence of mania; among alcohol-dependent women it is 6.8%.[19] Dually diagnosed patients have several negative outcomes, including higher rates of relapse, hospitalization, violence, incarceration, homelessness, and serious infections such as hepatitis and human immunodeficiency virus.[20,21] However, to our knowledge, substance abuse has been specifically assessed as a risk factor for ADM in only 1 study,[22] which found a positive association with ADM (OR = 6.99 for substance abuse history, 95% CI = 1.57 to 32.28, N = 53). In this report, we assess substance abuse as a risk factor for ADM, partly to replicate the previous study, but also to more validly assess this issue in an observational study in which confounding factors are adjusted for using regression modeling.

METHOD

Charts of all patients with bipolar disorder treated in an academic bipolar specialty clinic (Cambridge Health Alliance [CHA]; Cambridge, Mass.) from 2000 to 2004, roughly half as part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD),[23] were screened to identify all subjects treated with antidepressants. Waiver of consent was obtained by the CHA institutional review board for this chart review. Data were retrieved by 1 researcher (S.G.M.) and reviewed by 2 researchers (S.G.M. and S.N.G.). Data were harvested anonymously and entered into a computerized program, which was double-checked by 2 researchers (S.G.M. and T.B.P.). Data analyses were conducted using Statview and STATA Intercooled statistical software, version 8.0 (Stata Corp., College Station, Tex.).

Charts were reviewed for the following clinical and demographic variables: age; sex; family history of psychiatric disorders; psychiatric history, including age at onset of illness; current substance abuse and substance abuse history, including substance type; concurrent medications, including mood stabilizer use and dosage; evidence regarding poor response to standard mood stabilizers in the past; number of years ill; bipolar subtype; antidepressant type; number of antidepressant trials; and total number of mood episodes. Mood disorder diagnoses were based on the application of the Structured Clinical Interview for DSM-IV (SCID)[24] mood module by a psychiatrist with expertise in mood disorders (S.N.G.) and were made upon entry to treatment at the CHA bipolar clinic. All substance abuse diagnoses were defined using DSM-IV criteria applied upon entry to the CHA clinic and at all follow-up time points. Such diagnoses were reassessed by the investigators, applying DSM-IV criteria, at the time of the retrospective chart review.

The primary exposure was history of substance abuse, which could include current or past abuse. Current (at the time of chart review) substance abuse alone could not be assessed as a relevant predictor of ADM, since most antidepressant trials examined in this retrospective chart review occurred in the past, at which time those with current substance abuse may or may not have been abusing substances. A history of substance abuse is the most relevant predictor to analyze antidepressant trials in the past, which is why we made it our main predictor. The primary outcome was occurrence of a manic or hypomanic episode within 12 weeks of beginning an antidepressant trial, based on published definitions of this outcome.[15] We utilized all trials for all patients in this study, including all data for each subject without exception. No trial was excluded.

Upon entry to our clinic, all patients were evaluated with a systematic interview as part of standard procedures. The data analyzed in this study were assessed using a structured interview performed by trained clinician investigators experienced with the assessment and treatment of patients with bipolar disorder. Diagnoses were made upon entry to treatment at the CHA or Massachusetts General Hospital bipolar clinics, with half of the subjects entering via the STEP-BD study. The structured interviews assessed the following: current depressive and manic symptoms using DSM-IV criteria, current medications, past depression and mania using SCID mood

modules, number of previous mood episodes, history of substance abuse or dependence, previous treatment trials and response to them, medical history, and current mental status using a mental status examination. All interviewers were trained psychiatrists employed in academic bipolar specialty clinics that had been trained in procedures with adequate interrater reliability consistent with those of STEP-BD. Rapid cycling was defined as > 4 mood episodes in the previous year before evaluation. Past psychosis was defined as presence of delusions or hallucinations as defined in the SCID psychosis module. Diagnoses were based on application of DSM-IV criteria.

To diminish the impact of confounding bias on these observational data, we prepared the following a priori statistical analysis plan. Our primary outcome was the categorical occurrence of mania or hypomania within 12 weeks after onset of an antidepressant trial. Our primary predictor was presence or absence of lifetime substance abuse. After this univariate comparison using the χ^2 test, we planned an a priori multivariable logistic regression model, in which all of the variables collected above were included one by one in the model. Variables were retained in the model if they were independently statistically significant predictors of the outcome or if they appeared to exercise a confounding effect on the effect estimate for the primary predictor (lifetime presence of substance abuse), using the difference criterion of more than 10% magnitude change in relative risk.[25] All data are provided as odds ratios (ORs) with 95% confidence intervals (CIs), in accordance with the recommendations of the International Committee of Medical Journal Editors.[26] Consistent with the appropriate use of hypothesis-testing statistical methods,[25] only 1 p value is reported to test the single primary hypothesis of the study, the association between SUD and ADM.

Secondary analyses were conducted to test whether antidepressant type predicted ADM and to test whether substance type predicted ADM. Those analyses were conducted with multivariable regression modeling methods as described above. The specific covariates included in the final regression model used were age, gender, number of years ill, bipolar subtypes, type of antidepressant used, number of previous antidepressant trials, number of past mood episodes, family history of mental illness, the use of lithium, the use of valproate, the use of antipsychotics, and the presence of current substance abuse.

RESULTS

The sample consisted of 335 antidepressant trials in 98 patients with bipolar disorder. The sample was divided into those with and without substance use disorder, with 55 SUD patients, producing 184 trials, and 43 non-SUD patients, producing 151 trials. Current substance abuse was seen in 77 trials (42%). Individuals who displayed either lifetime substance abuse or lifetime substance dependence were grouped together in the substance use disorder category. In the 55 SUD patients, alcohol was the most frequently abused substance (N = 40), followed by marijuana (N = 27), cocaine (N = 13), amphetamines (N = 6), and opiates or sedatives (N = 5). Thirty-two patients (58.2%) engaged in polysubstance abuse, most commonly alcohol plus marijuana or cocaine (N = 12, 37.5% of the polysubstance abuse subgroup). Of 23 patients (41.8%) with single substance abuse, the most common was alcohol (N = 16, 69.6% of the single substance abuse group).

Baseline demographic and clinical characteristics of the sample are shown in Tables 1–3. As noted in the tables, there are a number of imbalances between the 2 groups that could represent confounding factors, particularly gender, bipolar subtype, and number of antidepressant trials. Also, there was greater lithium use in the SUD group and greater divalproex and antipsychotic use in the non-SUD group.

In the unadjusted univariate analysis, there was no relationship between SUD and ADM: ADM occurred in 20.7% of SUD trials and 21.4% of non-SUD trials.

However, in a multivariable regression model, there was a relationship between SUD and ADM (OR = 5.06, 95% CI = 1.31, 19.64; $p < .05$). Other apparent predictors of ADM were bipolar subtype (type II/NOS [not otherwise specified] more likely than type I, OR = 3.75 [1.21, 11.60]), gender (females more likely than males, OR = 4.25 [1.21, 15.00]), and antidepressant type (TCAs more likely than bupropion, OR = 5.12 [0.98, 26.83]; SRIs more likely than bupropion, OR = 2.85 [0.76, 10.77]). All of these predictors are adjusted for each other and all other variables in the final regression model.

DISCUSSION

In this observational study, we found 5-fold increased odds of antidepressant-induced mania in persons with lifetime substance use disorder. This finding suggests that RCTs of antidepressant use in bipolar disorder could systematically underreport ADM due to exclusion of patients with SUD. Other risk factors for ADM that were identified in the multivariable regression model were the type II subtype of bipolar illness, female gender, TCA use, and possibly SRI use (as opposed to bupropion).

Our results are almost identical to the previous report by Goldberg and Whiteside,[22] which found an OR of 6.99. Unlike the previous observational literature on other predictors of mania, this study corrected for a number of potential confounding factors using a regression model. An important effect was seen when correcting for concomitant medications, in particular antimanic and mood-stabilizing medications, which were unequally distributed in the SUD and non-SUD patients. Indeed, the association

Table 1. Clinical, Demographic, and Treatment Characteristics of the Sample (N = 335 trials)

Characteristic	SUD	No SUD
N (%)	184 (54.9)	151 (45.1)
Gender, male/female, %	52.2/47.8	29.1/70.9
Age, mean ± SD (range), y	44.3 ± 13.0 (18, 74)	39.1 ± 12.9 (19, 65)
Bipolar subtype, N		
I	143	113
II	27	21
NOS	14	17
Antidepressant-induced mania, yes/no, %	20.7/79.3[a]	21.4/78.6[b]
No. of antidepressant trials, mean ± SD (range)	4.6 ± 2.2 (1, 9)	5.2 ± 3.7 (1, 16)
Trial duration, median ± SD [95% CI], wk	12 [8.0, 24.0]	12 [8.0, 21.7]
Duration of illness, mean ± SD (range), y	28.2 ± 15.3 (6, 69)	24.8 ± 13.2 (2, 49)
Age at first MDE, mean ± SD (range), y	14.9 ± 7.8 (5, 35)	14.6 ± 6.2 (4, 35)
No. of MDEs, mean ± SD (range)	31.9 ± 16.9 (1.5, 50)	29.3 ± 18.4 (0, 50)
Age at first mania, mean ± SD (range), y	21.8 ± 9.3 (5, 47)	22.7 ± 6.4 (11, 47)
No. of manias/hypomanias, mean ± SD (range)	26.2 ± 19.9 (0, 50)	23.1 ± 19.4 (1, 50)
Age at onset of SUD, mean ± SD (range), y	20.7 ± 8.1 (12, 40)	NA
Antidepressant type[c], %		
Bupropion	16.9	17.3
SRI	50.0	52.7
TCA	6.0	8.7
Other	27.1	21.3
SUD treatment history, yes/no, %	41.9/58.1	NA
Family history of mental health diagnoses[d], %		
Bipolar disorder	49.1	48.8
Unipolar depression	38.2	32.6
Other	36.4	34.9
Mean no. of concomitant mood stabilizers or antipsychotics	1.38	1.53

[a]Missing N = 10.
[b]Missing N = 11.
[c]Information was missing for 1 patient in the No SUD group.
[d]Total patients who had a family history was 98: 55 in the SUD group and 43 in the No SUD group.
Abbreviations: MDE = major depressive episode, NA = not applicable, NOS = not otherwise specified, SRI = serotonin reuptake inhibitor, SUD = substance use disorder, TCA = tricyclic antidepressant.

Table 2. Concomitant Mood-Stabilizing or Antimanic Agent Use (%; N = 335 trials)

Agent	SUD (N = 184)	No SUD (N = 151)
Lithium	48.3	28.5
Divalproex	20.1	43.0
Lamotrigine	27.7	24.5
Topiramate	10.9	11.3
Gabapentin	9.2	11.0
Carbamazepine	2.7	7.3
Antipsychotics	11.4	31.8

Abbreviation: SUD = substance use disorder.

Table 3. Concomitant Antidepressant Use by Class (%; N = 335 trials)

Agent	SUD (N = 184)	No SUD (N = 151)
SSRI	50.0	52.3
Novel	34.2	27.8
TCA	9.2	12.6
Other	3.8	4.6
MAOI	2.2	2.6

Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, SUD = substance use disorder, TCA = tricyclic antidepressant.

between SUD and ADM did not become apparent until the potential confounders were controlled for in multivariable regression models. This observation of "negative confounding," when confounding factors obscure a real relationship so that univariate analyses are negative, may help explain why previous studies, which only used univariate analyses, reported conflicting results.

Limitations of the Study

This report has a number of limitations. First, these data are nonrandomized, but it should be noted that some confounding factors were controlled for in our statistical analysis. Second, treatment assessments partially involved the assessment of the treating clinician and were not blinded; thus, these data are open to measurement bias. Of note, however, is that any specific direction of bias in favor of one agent or the other would not appear to be present, as these patients were not treated with any study hypothesis in mind. Third, the frequent use of concomitant therapy may have obscured the real treatment effect of antidepressants. Despite this intrinsic limitation, data on concomitant mood stabilizer use, where available, were controlled for in the analysis. Fourth, adherence and compliance measurements were not available in the analysis. Lastly, not all relevant predictors of antidepressant-induced mania were assessed. For instance, we did not use rapid cycling as a predictor because most of the antidepressant trials had occurred in the past at the time of the

retrospective chart review. Since current rapid cycling would not necessarily be present in the past, we did not use current rapid cycling as a variable in our analyses. Nor did we have adequate data in the charts or from previous treatment before the patients entered our clinic to systematically determine whether rapid cycling was present in the past at each antidepressant trial. Thus, we could not assess the role of rapid cycling in this analysis.

It is always worthwhile to recall, in the context of these common limitations of observational studies, that such data, as opposed to those from randomized clinical trials, still have value in enhanced generalizability of findings compared with the special populations used in clinical trials. Prospective, controlled studies with larger sample sizes are needed to further confirm or refute these observations.

CONCLUSION

In this observational study, after some confounding factors were adjusted for, a history of substance abuse was a likely predictor for antidepressant-induced mania.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), divalproex (Depakote), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), topiramate (Topamax).

REFERENCES

1. Goodwin F, Jamison K. Manic Depressive Illness. New York, NY: Oxford University Press; 1990
2. Ghaemi SN, Rosenquist K, Ko J, et al. Effects of newer and older antidepressants in bipolar depression [abstract]. Bipolar Disord 2003; 5(suppl 1):49
3. Ghaemi SN, Sachs GS, Baldassano CF. Treatment-resistant bipolar disorder: clinical aspects and management. In: Pollack M, Rosenbaum JF, eds. Challenges in Psychiatric Treatment: Pharmacologic and Psychosocial Strategies. New York, NY: Guilford Press; 1996;53–88
4. Goldberg JF, Rabin A, Whiteside JE. Prevalence and risks associated with antidepressant-induced mania. In: New Research Program and Abstracts of the 154th Annual Meeting of the American Psychiatric Association; May 9, 2001; New Orleans, La. Abstract NR539
5. Henry C, Sorbara F, Lacoste J, et al. Antidepressant-induced mania in bipolar patients: identification of risk factors. J Clin Psychiatry 2001;62: 249–255
6. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry 1994;164:549–550
7. Truman C, Baldassano C, Goldberg J. History of antidepressant-induced mania in the STEP 500. In: New Research Program and Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif. Abstract NR29
8. Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry 2004;161:1537–1547
9. Mendlewicz J, Youdim MB. Antidepressant potentiation of 5-hydroxytryptophan by L-deprenil in affective illness. J Affect Disord 1980;2:137–146
10. Himmelhoch J, Fuchs C, Symons B. A double-blind study of tranylcypromine treatment of major anergic depression. J Nerv Ment Dis 1982;170:628–634
11. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003;60:1079–1088
12. Cohn JB, Collins G, Ashbrook E, et al. A comparison of fluoxetine, imipramine and placebo in patients with bipolar depressive disorder. Int Clin Psychopharmacol 1989;4:313–314
13. Nemeroff CB, Evans DL, Gyulai L, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001;158:906–912
14. Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials. New York, NY: Springer-Verlag; 1998
15. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. Bipolar Disord 2003;5:407–420
16. Rothman K, Greenland S. Modern Epidemiology. Philadelphia, Pa: Lippincott-Raven; 1998
17. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. JAMA 1990;264:2511–2518
18. Albanese MJ, Clodfelter RC Jr, Pardo TB, et al. Underdiagnosis of bipolar disorder in men with substance use disorder. J Psychiatr Pract 2006;12:124–127
19. Kessler RC, Crum RM, Warner LA, et al. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry 1997; 54:313–321
20. Albanese MJ, Pies R. The bipolar patient with comorbid substance use disorder: recognition and management. CNS Drugs 2004;18:585–596
21. Drake RE, Essock SM, Shaner A, et al. Implementing dual diagnosis services for clients with severe mental illness. Psychiatr Serv 2001;52: 469–476
22. Goldberg J, Whiteside J. The association between substance abuse and antidepressant-induced mania in bipolar disorder: a preliminary study. J Clin Psychiatry 2002;63:791–795
23. Sachs GS. Strategies for improving treatment of bipolar disorder: integration of measurement and management. Acta Psychiatr Scand Suppl 2004; 422:7–17
24. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV. New York, NY: Biometric Research, New York State Psychiatric Institute; 1995
25. Rothman KJ. Epidemiology: An Introduction. Oxford, England: Oxford University Press; 2002
26. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication updated October 2004. Mymensingh Med J 2005;14:95–119