

10-2009

Antidepressant-induced mania with concomitant mood stabilizer in patients with comorbid substance abuse and bipolar disorder.

Daniel Z Lieberman

George Kolodner

Suena H Massey

Kenneth P Williams

Follow this and additional works at: https://hsrc.himmelfarb.gwu.edu/smhs_psych_facpubs

 Part of the [Mental and Social Health Commons](#), [Psychiatry Commons](#), and the [Psychiatry and Psychology Commons](#)

APA Citation

Lieberman, D., Kolodner, G., Massey, S., & Williams, K. (2009). Antidepressant-induced mania with concomitant mood stabilizer in patients with comorbid substance abuse and bipolar disorder.. *Journal of addictive diseases : the official journal of the ASAM, American Society of Addiction Medicine*, 28 (4). <http://dx.doi.org/10.1080/10550880903182994>

This Journal Article is brought to you for free and open access by the Psychiatry and Behavioral Sciences at Health Sciences Research Commons. It has been accepted for inclusion in Psychiatry and Behavioral Sciences Faculty Publications by an authorized administrator of Health Sciences Research Commons. For more information, please contact hsrc@gwu.edu.

Antidepressant-Induced Mania with Concomitant Mood Stabilizer in Patients With
Comorbid Substance Abuse and Bipolar Disorder

Daniel Z. Lieberman, M.D.

Department of Psychiatry and Behavioral Sciences

George Washington University

Washington, DC

USA

George Kolodner, M.D.

Department of Psychiatry

Georgetown University

Washington, DC

USA

Suena H. Massey, M.D.

Department of Psychiatry and Behavioral Sciences

George Washington University

Washington, DC

USA

Kenneth P. Williams, M.D.

Department of Psychiatry and Behavioral Sciences

George Washington University

Washington, DC

USA

There was no financial support for this study. No part of this data has been presented at scientific meetings.

Acknowledgements

The authors thank Tamas Kelly, M.D. and Walter Brown, M.D. for comments on earlier drafts of this paper. The authors also thank Jackie Stackhouse for her assistance with this study.

Tamas Kelly, M.D. The Depression & Bipolar Clinic of Colorado. Dr. Kelly received no funding for his assistance. He has received honoraria from GlaxoSmithKline and AstraZeneca.

Walter Brown, M.D. Brown University and Tufts University School of Medicine. Dr. Brown received no funding for his assistance has no conflicts of interest to report.

Jackie Stackhouse. Kolmac Clinic. Ms. Stackhouse received no funding for her assistance and has no conflicts of interest to report.

Corresponding author:

Daniel Z. Lieberman, M.D.

Department of Psychiatry and Behavioral Sciences

George Washington University

2150 Pennsylvania Ave, NW

Washington, DC 20037

Tel: (202) 741-2899

Fax: (202-741-2891

Abstract

Objective: The role of antidepressants in the treatment of bipolar disorder is controversial due to the risks of affective switching and cycle acceleration. Studies of non-comorbid populations suggest that the risk of switching can be mitigated with the use of a concomitant mood stabilizer. The majority of patients with bipolar disorder, however, will experience a comorbid substance use disorder, and little is known about these individuals because they are typically excluded from clinical trials. We report on switch rates among bipolar patients recruited from a substance abuse specialty clinic.

Method: All patients entering treatment who had a history of antidepressant use were screened for bipolar disorder using the Mood Disorders Questionnaire. Those who screened positive completed a questionnaire on their psychiatric history, and were interviewed by telephone to confirm their diagnosis using DSM-IV criteria, and to document response to treatment. Third party informants were also interviewed.

Results: Eighty-seven individuals were enrolled between February 2007 and February 2008, and bipolar disorder was confirmed in 41. The total lifetime switch rate was 76%. When antidepressants were combined with a mood stabilizer, the switch rate was 56%. There was no difference between patients with bipolar I and bipolar II disorders. Some patients had more than one lifetime trial of combination treatment, primarily those who did not switch on initial exposure. The switch rate per trial was 35%.

Conclusion: A comorbid substance use disorder may be a relative contraindication to the use of antidepressants in bipolar disorder. Bipolar I and bipolar II patients reported high switch rates for both monotherapy and combination therapy.

Key words: Bipolar disorder, substance use disorder, antidepressant-induced mania, affective switching, bipolar depression

Introduction

Although antidepressants are commonly prescribed to patients with bipolar disorder,¹ the use of these medications remains controversial.² While antidepressants are unequivocally effective in the treatment of major depressive disorder, the evidence for efficacy in bipolar disorder is mixed.^{3,4} Safety concerns include the risk of cycle acceleration in which periods of euthymic mood are shortened following antidepressant use,⁵ and affective “switching,” in which patients with depression develop a manic, hypomanic, or mixed episode.⁶

Data on non-comorbid populations suggest that coadministration of an antimanic mood stabilizer prevents antidepressant-induced switching. A review of 12 randomized trials on the efficacy and safety of antidepressants in the treatment of bipolar depression found that patients who took an antidepressant plus a mood stabilizer had a switch rate no greater than those on placebo plus a mood stabilizer.⁷ The switch rate for subjects taking antidepressants was 3.8% compared to 4.7% for those taking placebo. Reliance on mood stabilizers to prevent affective switching caused by antidepressants is also reflected in treatment guidelines which place this combination high on the list of options recommended for the treatment of bipolar depression.^{8,9}

Risk factors for antidepressant-induced switching include multiple antidepressant trials,¹⁰ previous antidepressant-induced manias,¹¹ and comorbid substance use disorders.^{12,13} The majority of patients with bipolar disorder experience a substance use disorder at

some time during their lives, making the latter risk factor clinically important.¹⁴

Unfortunately, little empirical data exist to clarify the magnitude of the risk, in part because substance use disorders are a routine exclusion criteria for patients entering into clinical trials. Only two published studies have looked at this risk factor. A patient interview study of 53 patients with bipolar disorder which included 17 patients who had a history of a comorbid substance use disorder found that comorbid patients were more likely to have experienced an antidepressant-induced mania.¹² In this study switch rates on antidepressant monotherapy versus coadministration with a mood stabilizer were not separately reported for the comorbid group. The overall switch rate was 39.6%, and within this group, those with a history of a substance use disorder were approximately seven times more likely to have experienced a switch event compared to those without such a history.

A chart review study of 98 patients treated in a bipolar specialty clinic, 55 of whom had a comorbid substance use disorder, looked specifically at the use of the combination of an antidepressant and a mood stabilizer.¹³ In the unadjusted analysis antidepressant induced mania occurred in 20.7% of trials given to patients with a history of a substance use disorder, and 21.4% of trials given to those without a history of a substance use disorder. A multivariable regression model that controlled for clinical differences between the two groups found a five-fold increased odds of antidepressant-induced mania in the substance using group.

In this report we add to the limited research on this topic by evaluating history of antidepressant-induced switches in a group of patients recruited from a specialty clinic for substance use disorders. We report on rates of switches both with and without concomitant mood stabilizers. Patients with both bipolar I and bipolar II disorder were included in the analysis in order to shed light on the question of whether antidepressant treatment is safer in the latter group compared to patients with bipolar I disorder.

Method

Study participants were recruited from the Kolmac Clinic, a private outpatient treatment center for substance use disorders located in metropolitan Washington, DC. All patients entering treatment at the Kolmac Clinic were screened for psychiatric disorders during the initial evaluation. Patients who screened positive for probable bipolar disorder on the Mood Disorders Questionnaire (MDQ), using the standard cut off score of seven,¹⁵ and had a history of taking an antidepressant were offered participation in the study.

Patients who agreed to the informed consent were given a questionnaire in which they entered the following information: the names of all drugs of abuse used and the date of first use, history of diagnosis with depression and bipolar disorder, and the history of and clinical response to antidepressants and mood stabilizers. Subjects were also requested to provide contact information for a third party who knew them well, and to whom the subject was willing to have us speak about the subject's mood disorder. The purpose of

the third party contact was to attempt to identify manic, hypomanic, or mixed episodes that were not reported by the subjects.

Follow up interviews were done by telephone after the completion of the questionnaire. The purpose of the interview was to confirm a diagnosis of bipolar disorder, verify the accuracy of the information reported on the questionnaire, and obtain detailed information on the subject's history of treatment with antidepressants and mood stabilizers. All interviews were done by psychiatrists, and diagnoses were defined using DSM-IV criteria.

Establishing a diagnosis of bipolar disorder independent of symptoms of a substance use disorder can be challenging, and requires a careful evaluation of the nature and time course of the symptoms.¹⁶ The probability of the presence of bipolar disorder was evaluated based on the following: a clear history of a manic, hypomanic, or mixed episode prior to the onset of substance use; symptoms of abnormal mood that occurred during periods of abstinence from drug use; symptoms of abnormal mood that occurred episodically, clustered together, and cycled independently of the substance use; symptoms of abnormal mood that were qualitatively different from the usual symptoms of intoxication or withdrawal experienced by the patient; and a family history of bipolar disorder.¹⁷

In order for a switch to be coded as antidepressant-induced, it had to occur within 8 weeks of the initiation of antidepressant treatment. Switches that occurred on the

combination of an antimanic mood stabilizer and an antidepressant required that the patient had been taking one or more mood stabilizers at the time of antidepressant initiation.

An antimanic mood stabilizer was defined as a medication that is approved for the treatment of acute mania by the Food and Drug Administration (FDA), and included aripiprazole, carbamazepine, clozapine, divalproex/valproate, lithium, olanzapine, quetiapine, risperidone, and ziprasidone. Gabapentin, oxcarbazepine, topiramate, and other medications that have been reported to have mood stabilizing properties were not classified as mood stabilizers for the purposes of this study. Although lamotrigine is approved for the treatment of bipolar disorder, it was not included in the list of eligible mood stabilizers. Some studies have found it to be effective for the treatment of acute mania,^{18, 19} however, in general there is a consensus that it lacks a robust antimanic effect²⁰ and it does not have a FDA approval for this indication.

Third party interviews were conducted following the subject interviews. In order to minimize loss of privacy, third parties were only told that the subjects were part of a mood disorder study, and substance abuse was not inquired about, or brought up during the interview. Third parties were asked about the presence of symptoms of elevated mood, and were specifically asked to focus on times when antidepressants had been started.

The study was approved by the George Washington University Institutional Review Board.

Results

Between February 23, 2007 and February 17, 2008, 87 patients were enrolled who met the inclusion criteria, and gave informed consent to participate in the study. All of these subjects completed a questionnaire. Two subjects could not be reached for a follow up telephone interview. Of the remaining 85 subjects who participated in a telephone interview a diagnosis of bipolar I or II disorder was confirmed in 41. The average MDQ score of these subjects was 11.1 (SD=2.0), compared to 10.1 (SD=2.2) for the 44 subjects who were not found to have a diagnosis of bipolar disorder.

Table 1 shows the demographic and clinical characteristics of the bipolar patients. As per the inclusion criteria, all of them had taken an antidepressant, and 61% had been prescribed a medication approved for the treatment of bipolar disorder. Twenty-three patients had been prescribed an antidepressant medication while on an antimanic mood stabilizer. Table 2 lists the drugs of abuse reported by patients. The prescription drug use frequencies do not include therapeutic use.

Switch rates following antidepressant exposure are shown in Table 3. Overall, switch rates were high. Most patients had experienced an antidepressant-induced mania. Of

those who had ever taken a combination of an antidepressant and antimanic mood stabilizer, the switch rate was 56%.

Of the 23 patients in this study who had ever received an antidepressant plus an antimanic medication, 6 had more than one trial such that there were a total of 37 combination trials. Four of the 6 patients who had multiple trials never experienced a switch, and accounted for 7 of the 13 additional trials. One patient had three trials, and switched all three times, and one patient had five trials, and only switched following the final one. In total, there were 37 trials of an antidepressant plus a mood stabilizer and 13 switches giving a switch rate of 35%.

The risk of switching on the combination of an antidepressant and a mood stabilizer was not significantly correlated with a subject's age, gender, MDQ score, the MDQ seriousness item, or the number of substances they had misused. The number of subjects was too small to meaningfully analyze any association of the risk of switching with individual substances used or individual medications taken.

Of the 85 subjects interviewed, 34 provided contact information for a third party that could be successfully reached. In five of these cases the third party identified a manic, hypomanic, or mixed episode that led to either a change in diagnosis, or a change in the classification of whether or not the subject switched in response to an antidepressant or to an antidepressant and mood stabilizer combination.

Discussion

The percentage of patients who reported switching, that is, converting from a major depressive episode to a manic, hypomanic, or mixed episode, in response to the combination of an antidepressant and a mood stabilizer, was substantially higher than has been reported in studies of non-comorbid patients.⁷ There are a number of possible explanations for this finding.

Substances of abuse may have a toxic effect on the brain, thereby worsening the course of a comorbid mood disorder. Data has shown that compared to patients with non-comorbid bipolar disorder, those who also have a substance abuse disorder experience more severe pathology, and less favorable outcomes, including higher rates of mixed states, rapid cycling, impulsivity, aggression, and destabilization of sleep patterns.²² It is possible that substance abuse increases a patient's vulnerability to the mood destabilizing effects of an antidepressant, or decreases responsiveness to mood stabilizers.

Another possibility is that substance abuse is a marker of a bipolar disorder that is inherently more unstable. Patients with a more severe form of the illness may be more likely to self-medicate with substances of abuse, or seek the hedonic effects of substance use during periods of elevated mood.

Finally, the risks of substance abuse and antidepressant induced mania may both be expressions of an underlying neuropsychiatric abnormality. Drugs of abuse interact with

brain systems that are normally involved in the process of incentive, motivation, and reward.²² Disturbances in drug reward are mediated, in part, by dysregulated neural integration of dopamine and glutamate signaling in the nucleus accumbens.²³ Similar disturbances have been implicated in other psychiatric disorders, including bipolar disorder.^{24, 25} Patients with more severe pathology in these areas may be at greater risk for both substance abuse and mood instability. Genetic factors may also play a role in these types of disturbances. For example, Post and colleagues reported that bipolar patients with more chronic symptoms of abnormal mood were more likely to have a family history of substance abuse.²⁶

The MDQ had poor specificity in this sample. Only 48% of the patients who screened positive on the MDQ had a diagnosis of bipolar disorder confirmed by telephone interview. The average MDQ score of patients diagnosed with bipolar disorder was 11.1, compared to 10.1 for patients who were not given this diagnosis. This difference was not statistically significant. The original sample that was used to validate the MDQ recruited patients from mood disorder specialty clinics, and found a specificity of 0.90.¹⁵ A general population study also found a high specificity of 0.972, however the sensitivity in this sample was low.²⁷ Symptoms of intoxication can closely mimic symptoms of mania, and the MDQ does not ask respondents to attempt to identify the etiology of their symptoms, only to document the presence or absence of them over the course of the respondent's entire history. Consequently, it is not surprising that there were more false positives than true positives in this sample, and the results support the need to screen for comorbid substance abuse when interpreting a positive MDQ. Only patients with a positive MDQ

screen were included in this study, therefore the sensitivity could not be calculated in this sample.

Even for a trained diagnostician, one of the challenges of the cross-sectional, retrospective nature of this study was making an accurate diagnosis of bipolar disorder in the context of a co-occurring substance use disorder. Correct diagnoses are most readily made when a patient can be observed longitudinally, especially during extended periods of abstinence.²⁸ In order to increase the accuracy of the diagnosis, all interviews were performed by psychiatrists, and an emphasis was placed on evaluating the time course of symptoms, whether the apparent symptoms of elevated mood were qualitatively different from those of substance intoxication, and whether the mood symptoms cycled independently of substance use patterns.

As noted above, efforts to carefully distinguish symptoms of bipolar disorder from symptoms of a substance use disorder resulted in more than half of the patients who had a score of seven or more on the MDQ being classified as not having bipolar disorder. Because of the substantial risk of misdiagnosis in comorbid patients, a high degree of confidence in the diagnosis of bipolar disorder was required for a patient to be included in the analysis. This may have led to a bias toward patients with more classic or more severe manifestations of bipolar disorder, which may in turn have resulted in the recruitment of a sample more likely to have experienced an antidepressant-induced switch.

Two analyses were performed. The percentage of patients who experienced a switch on the combination of an antidepressant and mood stabilizer (56%), and the percentage of antidepressant plus mood stabilizer trials that resulted in a switch (35%). The first analysis would tend to overestimate the true risk because some of the patients had more than one trial, but did not switch every time. A clinician would be more interested in the risk of switching with a specific trial rather than the lifetime risk in the context of multiple trials.

The second analysis is more comparable to the non-comorbid literature in which the risk was assessed in the context of a single clinical trial. This analysis, however, in the current study may underestimate the true risk. Patients who do not switch as a result of past trials may be more likely to receive future trials. Conversely, patients who do switch would be less likely to be given an antidepressant in the future. This tendency would mean that the least vulnerable patients would receive the most trials. In spite of the potential bias toward underestimation in this type of analysis, the risk was nevertheless nine times higher than has been reported in non-comorbid samples.⁷

The lifetime rate of any switch, whether in combination with a mood stabilizer or not was 76%. This rate is substantially higher than found in other studies that did not specifically focus on substance abusing patients. A similar analysis from the STEP-BD program, in which self-reported histories of antidepressant-induced switching were evaluated retrospectively, found a lifetime switch rate of 44%.¹⁰ The STEP-BD sample included some patients with substance abuse histories, however the results were not reported

separately for these patients. Although some studies have reported comparable switch rates on or off mood stabilizers, patients in this study had lower rates when being treated with combined therapy. This difference was seen in patients with both bipolar I and bipolar II, suggesting that in this population of substance abusers, antidepressant monotherapy is contraindicated in both diagnostic groups.

This study has a number of limitations. There was no comparison group of patients without comorbid substance abuse. As a result, the high switch rate seen in this population may not be solely attributable to the presence substance abuse. There may have been other characteristics of this population that made them vulnerable to antidepressants. Another consequence of the absence of a comparison group was that the assessment was not blinded, and the data may have been affected by measurement bias. Additionally, the collection of data was dependent upon the memory of patients, and may have been subject to recall bias.

Despite the significant limitations, in the context of the poverty of literature with regard to substance use disorders as a risk factor for antidepressant-induced switching, this type of retrospective data can contribute to generalizable conclusions about the role of antidepressants in the treatment of comorbid bipolar patients. The highest quality data would require a randomized, double-blind, placebo-controlled design, however, this type of study would be difficult given the ethical constraints of double-blind studies.²⁹ In order to preserve patient safety, those who developed early symptoms of switching would have

to discontinue study medication, and receive treatment for these symptoms, precluding the use syndromal manic, hypomanic, or mixed states as an outcome measure.

The appropriate role of antidepressants in the treatment of bipolar disorder remains to be conclusively established. While the risk of induction of rapid cycling, and other forms of long-term destabilization is largely unknown with the newer antidepressants, much of the literature supports the belief that the short-term risk of switching can be adequately managed with the concomitant use of a mood stabilizer. The data that supports this treatment strategy is derived primarily from non-comorbid samples, however the high prevalence of substance use disorders among individuals with bipolar disorder, suggests that those results may not necessarily generalize to more typical clinical environments. The results of this study support the use of caution when prescribing antidepressants, even when given with a mood stabilizer, and a history of substance use disorder may be a relative contraindication to the use of this treatment strategy.

References

1. Goodwin FK, Jamison KR: Manic Depressive Illness: Bipolar Disorders and Recurrent Depression. New York, NY, Oxford University Press, 2007
2. Goldberg JF, Truman CJ: Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord* 2003; 5(6):407-20
3. Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME: Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 2007; 356(17):1711-22
4. Goldberg JF, Perlis RH, Ghaemi SN, Calabrese JR, Bowden CL, Wisniewski S, Miklowitz DJ, Sachs GS, Thase ME: Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. *Am J Psychiatry* 2007; 164(9):1348-55
5. Wehr TA, Goodwin FK: Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry* 1979; 36(5):555-9
6. Wehr TA, Goodwin FK: Can antidepressants cause mania and worsen the course of affective illness? *Am J Psychiatry* 1987; 144:1403-1411
7. Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM: Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry* 2004; 161(9):1537-47

8. Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP: The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. *Postgrad Med* 2000; Spec No:1-104
9. Suppes T, Dennehy EB, Hirschfeld RM, Altshuler LL, Bowden CL, Calabrese JR, Crismon ML, Ketter TA, Sachs GS, Swann AC: The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry* 2005; 66(7):870-86
10. Truman CJ, Goldberg JF, Ghaemi SN, Baldassano CF, Wisniewski SR, Dennehy EB, Thase ME, Sachs GS: Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *J Clin Psychiatry* 2007; 68(10):1472-9
11. Fogelson DL, Bystritsky A, Pasnau R: Bupropion in the treatment of bipolar disorders: the same old story? *J Clin Psychiatry* 1992; 53(12):443-6
12. Goldberg JF, Whiteside JE: The association between substance abuse and antidepressant-induced mania in bipolar disorder: a preliminary study. *J Clin Psychiatry* 2002; 63(9):791-5
13. Manwani SG, Pardo TB, Albanese MJ, Zablotsky B, Goodwin FK, Ghaemi SN: Substance use disorder and other predictors of antidepressant-induced mania: a retrospective chart review. *J Clin Psychiatry* 2006; 67(9):1341-5
14. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK: Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *Jama* 1990; 264(19):2511-8

15. Hirschfeld RM, Williams JB, Spitzer RL, Calabrese JR, Flynn L, Keck PE, Jr., Lewis L, McElroy SL, Post RM, Rappaport DJ, Russell JM, Sachs GS, Zajecka J: Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry* 2000; 157(11):1873-5
16. Kranzler HR, Rosenthal RN: Dual diagnosis: alcoholism and co-morbid psychiatric disorders. *Am J Addict* 2003; 12 Suppl 1:S26-40
17. Weiss RD: identifying and diagnosing co-occurring disorders. *CNS Spectrums* 2008; 13(4(suppl 6)):1-16
18. Ichim L, Berk M, Brook S: Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. *Ann Clin Psychiatry* 2000; 12(1):5-10
19. Berk M: Lamotrigine and the treatment of mania in bipolar disorder. *Eur Neuropsychopharmacol* 1999; 9 Suppl 4:S119-23
20. Lieberman DZ, Goodwin FK: Separate and concomitant use of lamotrigine, lithium, and divalproex in bipolar disorders. *Current Psychiatry Reports* 2004; 6(6):459-465
21. Goodwin FK, Jamison KR: Comorbidity, in *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression*. New York, NY, Oxford University Press, 2007, pp 223-245
22. Robinson TE, Berridge KC: Incentive-sensitization and addiction. *Addiction* 2001; 96(1):103-14
23. Chambers RA, Krystal JH, Self DW: A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biol Psychiatry* 2001; 50(2):71-83

24. Blumberg HP, Kaufman J, Martin A, Whiteman R, Zhang JH, Gore JC, Charney DS, Krystal JH, Peterson BS: Amygdala and Hippocampal Volumes in Adolescents and Adults With Bipolar Disorder. *Arch Gen Psychiatry* 2003; 60(12):1201-1208
25. Pearlson GD, Wong DF, Tune LE, Ross CA, Chase GA, Links JM, Dannals RF, Wilson AA, Ravert HT, Wagner HN, Jr, et al: In vivo D2 dopamine receptor density in psychotic and nonpsychotic patients with bipolar disorder. *Arch Gen Psychiatry* 1995; 52(6):471-477
26. Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, Rush AJ, Keck PE, Jr., McElroy SL, Luckenbaugh DA, Pollio C, Kupka R, Nolen WA: Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. *J Clin Psychiatry* 2003; 64(6):680-90; quiz 738-9
27. Hirschfeld RM, Holzer C, Calabrese JR, Weissman M, Reed M, Davies M, Frye MA, Keck P, McElroy S, Lewis L, Tierce J, Wagner KD, Hazard E: Validity of the mood disorder questionnaire: a general population study. *Am J Psychiatry* 2003; 160(1):178-80
28. Hendrickson EL, Schmal MS, Ekleberry SC: Assessment, in *Treating Co-Occurring Disorders: a Handbook for Mental health and Substance Abuse Professionals*. Binghamton, NY, Haworth Press, 2004, pp 77-95
29. Sachs G: Advances in the treatment of acute bipolar depression, in *Advances in the Treatment of Bipolar Disorders*. Washington, DC, American Psychiatric Association, 2005

Table 1. Clinical and Demographic Information (n=41). Continuous measures shown as averages with standard deviations in parentheses. Discreet measures are shown as the number of patients with percentages in parentheses.

Age	39.0 (SD=11.0)
Male	20 (49%)
Female	21 (51%)
Lifetime number of drugs of abuse	4.2 (SD=2.2)
MDQ score	11.1 (SD=2.0)
Bipolar I	18 (44%)
Bipolar II	23 (56%)
Lifetime use of an antidepressant	41 (100%)
Lifetime use of an FDA approved medication for bipolar disorder	25 (61%)
Received an antidepressant while on an antimanic medication	23 (56%)

Table 2. Lifetime history of substances abused by bipolar subjects (n=41).

Drug	N (%)
Alcohol	40 (97.6)
Cannabis	36 (87.8)
Cocaine	24 (58.5)
Methylenedioxymethamphetamine (Ecstasy)	17 (41.5)
Lysergic acid diethylamide (LSD)	12 (29.3)
Ketamine	9 (22.0)
Benzodiazepines	7 (17.1)
Methamphetamine	7 (17.1)
Prescription opioids	7 (17.1)
Heroin	6 (14.6)
Phencyclidine (PCP)	4 (9.8)
Prescription stimulants	4 (9.8)

Table 3. Lifetime history of experiencing a mood switch from a major depressive episode to a manic, hypomanic, or mixed episode in response to an antidepressant trial.

Diagnosis	Switch Rate
With or without a concomitant antimanic medication	
Bipolar I and II	31 of 41 (76%)
Bipolar I	15 of 18 (83%)
Bipolar II	16 of 23 (70%)
In combination with an antimanic medication	
Bipolar I and II	13 of 23 (56%)
Bipolar I	8 of 14 (57%)
Bipolar II	5 of 9 (56%)