Published in final edited form as:

Am J Addict. 2010 ; 19(5): 440–449. doi:10.1111/j.1521-0391.2010.00060.x.

Independent Predictors for Lifetime and Recent Substance Use Disorders in Patients with Rapid Cycling Bipolar Disorder: Focus on Anxiety Disorders

Keming Gao, MD, PhD¹, Philip K. Chan, MS¹, Marcia L. Verduin, MD², David E. Kemp, MD¹, Bryan K. Tolliver, MD, PhD², Stephen J. Ganocy, PhD¹, Sarah Bilali, MS¹, Kathleen T. Brady, MD, PhD², Robert L. Findling, MD¹, and Joseph R. Calabrese, MD¹

¹ Department of Psychiatry, Bipolar Disorder Research Center at Mood Disorders Program, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center, Cleveland, Ohio

² Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina

Abstract

We set out to study independent predictor(s) for lifetime and recent substance use disorder (SUDs) in patients with rapid cycling bipolar disorder (RCBD). Extensive Clinical Interview and Mini International Neuropsychiatric Interview were used to ascertain DSM-IV Axis I diagnoses of RCBD, anxiety disorders, and SUDs. Data from patients enrolling into four similar clinical trials were used. Where appropriate, univariate analyses with t-test or Chi-Square were applied. Stepwise logistic regression was used to examine the relationship among predictor variables and lifetime and recent SUDs. Univariate analysis showed that patients with co-occurring anxiety disorders (n=261) had significantly increased rates of lifetime (OR=2.1) and recent (OR=1.9) alcohol dependence as well as lifetime (OR=3.4) and recent (OR=2.5) marijuana dependence compared to those without co-occurring anxiety disorder (n=303). In logistic regression analyses,

Address correspondence to Dr. Gao, 10524 Euclid Avenue, 12th floor, Cleveland, OH 44106. keming.gao@uhhospitals.org. Dr. Verduin is currently at the Department of Medical Education, University of Central Florida, College of Medicine in Orlando, Florida.

Declaration of Interest

Dr. Gao receives or has received, acted as a consultant and/or served on a speaker's bureau for Abbott, AstraZeneca, Pfizer, Schering-Plough, and NARSAD.

Dr. Verduin has received grant support from Bristol-Myers Squibb, Eli Lilly, and Janssen.

Dr. Kemp serves on the speaker's bureau for Astra-Zeneca and Pfizer, and serves as a consultant for Bristol-Myers Squibb. He has received research support from Takeda (study medication only, no financial support), NARSAD, and the International Society for Bipolar Disorders Research Fellowship Award; KL2 RR024990

Dr. Tolliver receives grant support from Forest Laboratories.

Dr. Ganocy Received grant support from Eli Lilly Co.

Dr. Findling receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Abbott, Addrenex, AstraZeneca, Biovail, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, KemPharm Lilly, Lundbeck, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Sanofi-Aventis, Sepracore, Shire, Solvay, Supernus Pharmaceuticals, Validus, and Wyeth.

Dr. Calabrese has received federal funding from the Department of Defense, Health Resources Services Administration and National Institute of Mental Health. He has received research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Cleveland Foundation, Eli Lilly, GlaxoSmithKline, Janssen, NARSAD, Repligen, Stanley Medical Research Institute, Takeda and Wyeth. He consulted to or served on advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo, EPI-Q, Inc., Forest, France Foundation, GlaxoSmithKline, Janssen, Johnson and Johnson, Lundbeck, Neurosearch, OrthoMcNeil, Otsuka, Pfizer, Repligen, Schering-Plough, Servier, Solvay, Supernus, Synosia, and Wyeth. He has provided CME lectures supported by Abbott, AstraZeneca, Bristol-Myers Squibb, France Foundation, GlaxoSmithKline, Janssen, Johnson and Johnson, Sanofi Aventis, Schering-Plough, Pfizer, Solvay, and Wyeth.

The other authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

generalized anxiety disorder (GAD) was associated with increased risk for lifetime SUDs (OR=2.34), alcohol dependence (OR=1.73), and marijuana dependence (OR=3.36), and recent marijuana dependence (OR=3.28). A history of physical abuse was associated with increased risk for lifetime SUDs (OR=1.71) and recent marijuana dependence (OR=3.47). Earlier onset of first mania/hypomania was associated with increased risk for lifetime SUDs (5% per year) and recent marijuana dependence (12% per year) and later treatment with a mood stabilizer were also associated with increased risk for recent SUDs (8% per year). Positive associations between generalized anxiety disorder, later treatment with a mood stabilizer, and early childhood trauma and history of SUDs suggests that adequate treatment of comorbid anxiety, early treatment with a mood stabilizer, and prevention of childhood trauma may reduce the risk for the development of SUDs in patients with bipolar disorder.

Introduction

Epidemiologic and clinical studies have shown that the rates of co-occurring anxiety disorders and substance use disorders (SUDs) are elevated in patients with bipolar disorder compared to those in the general population.^{1–11} Association between the presence of anxiety disorders and the increased risk of SUDs in bipolar patients has been reported.^{11–18} However, only a few studies have explored the association between individual anxiety disorders and more than one SUD in bipolar patients.^{14,16} Differential association between alcohol dependence and generalized anxiety disorder (GAD),¹⁶ cocaine/stimulant dependence and posttraumatic stress disorder (PTSD)^{14,16} were observed in bipolar individuals, but only lifetime prevalence rates of SUDs were used in these two studies. Only one study included all SUDs,¹⁴ but the study population was limited to patients who had substance dependence and continued using a substance in the 60 days prior to the initial assessment. To our knowledge, there has never been a study to investigate the association between anxiety disorders and lifetime and recent prevalence of each individual SUD in patients with bipolar disorder.

Previously, we found that the increased rates of GAD and panic disorder, but not obsessive compulsive disorder (OCD), only occurred in patients with rapid cycling bipolar I disorder (RCBDI) and co-occurring SUDs, not in those with RCBDI without a history of SUDs or in those with rapid cycling bipolar II disorder (RCBDII).¹⁹ However, among patients with RCBD and a recent history of SUDs, patients with either subtype had more similarities than differences in the rates of historical clinical variables, the number of SUDs, scores on the addiction severity index, and scores of global assessment scale.²⁰ Higher rates of SUDs in bipolar I than in bipolar II disorder were also reported in national epidemiologic studies.^{8,11} It remains unclear whether co-occurring anxiety disorders in patients with bipolar I or II disorder and other clinical variables have different associations with individual SUDs. Therefore, we utilized data from an initial assessment of patients with RCBDI or RCBDII who participated in four similar clinical trials to study interactions between co-occurring anxiety disorders and SUDs.

Methods

Patient Population

Data from the initial assessment of a cohort of patients with RCBD who were recruited for four randomized, double-blind, placebo-controlled clinical trials^{21,22} (www.clinicaltrials.gov, NCT00221975 & NCT00063362) were examined. These studies were conducted to assess the efficacy of different pharmacologic regimens for managing the acute and maintenance treatment of RCBD with or without a “recent” history of SUD, in which all patients were treated with divalproex and lithium initially in an open-label phase.

A “recent” SUD was defined as having a diagnosis of substance dependence and continuing to meet abuse or dependence criteria for a substance(s) in the last 6 months at the time of initial assessment or having a diagnosis of substance abuse and continuing to abuse a substance(s) in the previous 3–6 months. The study design, inclusion and exclusion criteria, mood state at study entry, and the stage of each study at the time of this analysis are summarized elsewhere.^{19,23}

Initial Assessments

The procedures for the initial assessment have also been described in detail previously.^{19,20,23} Briefly, the DSM-IV Axis I diagnoses of RCBD, anxiety disorders including GAD, panic disorder, and OCD, and SUDs were ascertained by extensive clinical interview alone²¹ and with the Mini-International Neuropsychiatric Interview (MINI)²⁴ by research psychiatrists and research assistants. The extensive clinical interview consists of questions and criteria for the diagnosis of DSM-IV Axis I disorders, which is similar to the Structured Clinical Interview for the DSM-IV, Patient Edition (SCID-I/P),²⁵ but also contains items to assess mental status, demographics, and other variables of interest. For the diagnosis of SUDs, the SCID-I/P substance use disorder module was used instead of the MINI. Collateral information from the mandatory presence of a patient’s significant other(s) was required in all cases during the initial assessment.

The age at onset of a first manic/hypomanic and depressive episode was retrospectively determined after the criteria for each of these episodes was explained to patients. The number of episodes of manic/hypomanic and depressive episodes in last 12 months was directly inquired. Each patient must have experienced ≥ 4 DSM-IV defined episodes of a major depressive, manic, mixed, or hypomanic episode and must be demarcated by either a period of full remission or by a switch to an episode of the opposite polarity. However, for those who also had episodes that met the symptom criteria, but not the duration with a switch to an episode of the opposite polarity, these episodes were counted into the total episodes in the last 12 months.

The time to first mood stabilizer treatment was determined by the time from first onset of mania/hypomania to the first time of a mood stabilizer treatment or ECT for manic or hypomanic symptoms. The mood stabilizers for mania/hypomania were defined as lithium, divalproex/valproic acid, carbamazepine, typical and atypical antipsychotics.

Experience of early life trauma was inquired about with the question of “Have you ever been physically, verbally, or sexually abused?” If a patient answered “yes,” then the patient was asked how and when the abuse occurred and who the perpetrator(s) was. No attempt was made to assess the severity of abuse. Other historical variables were also collected during the initial assessment.

Procedures

Data from the four studies were merged into one dataset. In one study²¹ and the early phase of another study,²² not all anxiety disorders or other Axis I disorders were assessed. Therefore, history of social phobia and posttraumatic stress disorder (PTSD) were not available for the analyses. The rates of co-occurring SUDs were compared according to the presence or absence of a lifetime history of anxiety disorders (e.g., GAD, panic disorder, and/or OCD) was present. “Any” SUD refers to the presence of alcohol or drug (legal or illegal) abuse or dependence except for caffeine and nicotine. Lifetime SUD refers to meeting the DSM-IV criteria of a SUD prior to or at the time of initial assessment. “Recent” SUD refers to meeting the DSM-IV criteria of a SUD as defined by the protocol.^{19,20}

Statistical Analysis

Univariate analyses were carried out to compare the differences between patients with and without a history of anxiety disorder(s), which provided a comparison with prior studies using similar techniques. Stepwise logistic regression was used to identify independent predictors of the probability for lifetime and recent SUDs. T-tests were used to evaluate continuous variables, with standard deviations to reflect the magnitude of variance. Chi-square tests were used to evaluate categorical data, with odds ratios (OR) as a risk estimate and 95% confidence interval (CI) to reflect the magnitude of variance. Given the exploratory nature of the study, two-tailed tests were set at $\alpha = 0.05$ for univariate analyses, in order to detect potential associations. Therefore, no adjustment was made for multiple comparisons.

For the regression analysis, multicollinearity was assessed prior to each model building process. If there was high collinearity between two variables, the variable with the least clinical significance was removed prior to the model building process. After the assessment of multicollinearity, the remaining variables were considered candidate independent variables for the stepwise logistic model building process.

Before starting the stepwise process, 5 specific potential confounders were to remain in the model building process. Gender and bipolar subtypes were justified to maintain in the model regardless of other variables because previous studies showed that gender and bipolar subtypes played a different role in comorbid SUDs in bipolar disorder.^{11,12,20} Similarly, GAD, panic disorder, and OCD were also maintained in the model. The intent of this was to more accurately study the predictive value of each individual anxiety disorders in the association with SUDs. In addition, an alpha level of 0.10 was set in order to detect potential associations.

There were 17 common variables among all the models, which included bipolar I subtype (yes/no), male gender (yes/no), age at study entry, the age onset of first mania/hypomania, the number of manic/hypomanic episodes in the last 12 months, the number of depressive episode in the last 12 months, the time to first mood stabilizer treatment, the age onset of first depressive episode, any anxiety disorder (yes/no), GAD (yes/no), OCD (yes/no), panic disorder (yes/no), physical abuse (yes/no), sexual abuse (yes/no), verbal abuse (yes/no), psychosis (yes/no), and an interaction term between GAD and panic disorder. Additional variables were added during different model building processes.

Results

Demographics

Of the 568 patients with RCBD, 564 of them were eligible for univariate analyses (RCBDI, $n=320$; RCBDII, $n=244$) with 261 having a lifetime history of GAD, panic disorder, and/or OCD. The mean age at study entry for the entire sample was 36.4 ± 10.4 years. Patients with anxiety disorder(s) were significantly younger than those without anxiety disorder(s). There was no gender difference between patients with and those without anxiety disorder(s) (Table 1).

Patients with versus without anxiety disorders as a group

As shown in Table 1, patients with RCBDI had significantly higher rates of anxiety disorders compared to those with RCBDII. As a group, there was a significant difference in the “any recent SUD” category between the patients with and those without anxiety disorder(s). Patients with anxiety disorder(s) also had significantly higher rates of lifetime alcohol and marijuana dependence compared to those without anxiety disorder(s). Patients

with anxiety disorder(s) also had significantly higher rates of recent alcohol and marijuana dependence compared to those without anxiety disorder(s).

Predictors for a lifetime history of SUDs

Initially, 20 potential predictors (17 common variables plus alcohol use disorder, alcohol abuse, and drug use disorder) were examined. However during the initial model building process, the number of mania/hypomania and the time of first mood stabilizer treatment of mania/hypomania were removed because they expressed high collinearity with the number of depressive episodes in the last 12 months and the age onset of first mania/hypomania, respectively. In addition, the variables alcohol use disorder, alcohol abuse, and drug use disorder were removed because they contained cell counts of zero. If these variables were included in the model, it would result in infinite values in the ORs as well as their confidence intervals. In total, before the stepwise logistic regression was performed, 5 of the 20 original variables were removed. Of the 568 patients, 446 had complete data on all 15 variables and 122 had a missing value on one or more variables. The most commonly missed data were a history of sexual abuse (n=73).

After the stepwise procedure, of 15 variables considered as candidate independent predictors, 4 variables were retained in the final model in addition to the 5 variables which were previously decided to remain in the model regardless of their statistical significance. These 4 variables were the age onset of first mania/hypomania, history of any anxiety disorder, physical abuse, and psychosis. Of these 9 variables, male gender, a history of GAD, physical abuse, and psychosis, and early onset of mania were significantly associated with an increased risk for a lifetime SUD(s) after controlling other variables (Table 2).

Predictors for a recent history of SUD

In the predictor for recent SUD analysis, the same 20 potential variables as lifetime SUDs were examined with 442 participants having complete data. A similar model building process as the predictors for lifetime history was used. The number of mania/hypomania in the last 12 month was removed from the model because of a high collinearity with the number of depressive episodes in the last 12 months. Of the 19 variables evaluated, bipolar I subtype, age at the study entry, time to first mood stabilizer treatment, a history of alcohol use disorder, drug use disorder, any anxiety disorder, and physical abuse were significantly associated with an increased risk for a recent SUD. However, a history of sexual abuse was negatively associated with the risk for recent SUDs (Table 2).

Predictors for a lifetime or recent history of alcohol dependence

In the predictor analysis for lifetime alcohol dependence, 18 variables (17 common variables plus drug use disorder) were examined. Variables of alcohol use disorder and alcohol abuse were not available because alcohol dependence was used as a dependent variable in this analysis. The number of mania/hypomania in the last 12 months was removed from the model because of the high collinearity with the number of depressive episodes in the last 12 months. Of the 17 variables considered as independent predictors, 422 of 568 patients had complete data. After the stepwise process, age at the study entry and history of drug use disorder remained in the model in addition to the 5 pre-determined important predictors (Table 3). A lifetime drug use disorder, male gender, bipolar I subtype, GAD, and age at study entry were associated with increased risk for lifetime alcohol dependence (Table 3).

Of the same 17 variables any anxiety disorder, bipolar I subtype, a history of drug use disorder was significantly associated with increased risk with recent alcohol dependence. A later treatment of mania/hypomania with a mood stabilizer was associated with a trend

increase in risk for recent alcohol dependence; however, a history of sexual abuse was associated with a trend decrease in the risk for recent alcohol dependence (Table 3).

Predictors for a lifetime and recent marijuana dependence

Similarly, 422 of 568 patients were eligible for both lifetime and recent marijuana dependence analyses. A total of 22 variables (17 common variables plus alcohol use disorder, alcohol abuse, cocaine dependence, cocaine abuse, and cocaine dependence*cocaine abuse) were examined. The number of mania/hypomania in the last 12 month was removed because of its high collinearity with the number of depressive episodes in the last 12 month. Therefore, 21 variables were considered in both models.

A lifetime history of cocaine dependence or abuse, GAD, bipolar I subtype, and a younger age at study entry were significantly associated with the increased risk for lifetime marijuana dependence (Table 4). Bipolar I subtype, a history of physical abuse, GAD was significantly associated with increased risk for recent marijuana dependence. Late onset of depression was positively associated with increased risk for recent marijuana dependence, but late onset of first mania or older age at study entry was negatively associated with increased risk for recent marijuana dependence (Table 4).

Predictors for a lifetime and recent cocaine dependence

Similar to alcohol and marijuana dependence, 422 of 568 patients were eligible for both lifetime and recent cocaine dependence analyses. A total of 22 variables (17 common variables plus alcohol dependence, alcohol abuse, marijuana dependence, marijuana abuse, and marijuana dependence*abuse) were examined. The number of depressive episodes in the last 12 months was removed because of its high collinearity with the number of mania/hypomania in the last 12 months. As in the model for marijuana dependence analyses, 21 variables were considered as candidates

A lifetime history of marijuana dependence or abuse, bipolar I subtype, the number of mania/hypomania in the last 12 months were independently associated with increased risk of lifetime cocaine dependence. A history of sexual abuse was associated with a trended increase in the risk for lifetime cocaine dependence (Table 5). In contrast to lifetime cocaine dependence, only lifetime alcohol abuse disorder was significantly associated with increased risk for a recent history of cocaine dependence. Male gender and a history of marijuana abuse were associated with trended increases in the risk for recent cocaine dependence (Table 5).

Discussion

To our knowledge, this is the first report to study the independent associations between anxiety disorders and SUDs in bipolar disorder by controlling for other potential confounding factors through regression analyses. A history of any anxiety disorder was associated with increased risk for a recent SUDs and recent alcohol dependence. Among the individual anxiety disorders, only a history of GAD was independently associated with the increased risk for a lifetime SUDs, lifetime alcohol dependence, and lifetime and recent marijuana dependence. On the other hand, a history of OCD was associated with the trended decrease in the risk for lifetime SUDs and lifetime marijuana dependence. In contrast, a history of panic disorder was not independently associated with any SUD.

The finding of patients with co-occurring anxiety disorders had a greater severity of SUDs than those without anxiety disorders (Table 1) is consistent with previous studies.^{16,17} The higher risk for alcohol dependence in those with comorbid any anxiety disorder has also been observed in other bipolar studies,^{16,17} however, this is the first study to report that

bipolar patients with GAD had a significantly higher risk for marijuana dependence than those without GAD even after controlling potential confounding factors. Due to the retrospective nature of our study, a causal relationship between GAD and alcohol or marijuana dependence could not be established. Longitudinal studies in non-bipolar populations have shown that there is a reciprocal causal relationship between alcohol dependence and anxiety disorders.^{26,27} In addition, self-medication behavior with alcohol or drugs has been observed in patients with primary anxiety disorders.^{28–30} In the National Comorbidity Survey-Replication study,²⁸ the onset of anxiety disorders were earlier than the substance use disorders. It is possible that the increased risk for alcohol and marijuana dependence in patients with GAD might be the consequence of self-medication. Clearly, longitudinal prospective study is warranted to confirm or refute this finding.

The finding of the trended decrease in the risk for the lifetime SUDs and recent marijuana dependence in patients with a history of OCD was unexpected as well as the lack of association between a history of panic disorder and any SUD. These results should be interpreted with caution since the prevalence rate of obsessive compulsive disorder in this sample were low, about 8% in patients with bipolar I disorder and 7% with bipolar II disorder.¹⁹ Therefore, the sample size might not be large enough to detect significant associations. In terms of panic disorder, preclinical and clinical studies have shown that cocaine is a powerful anxiogenic agent.^{31–33} It is quite possible that patients with GAD, panic disorder, and/or OCD did not have a higher risk of cocaine use disorders than those without three anxiety disorders simply due to the unwanted anxiogenic effect from cocaine. However, several studies have shown that patients with primary PTSD are more likely to self-medicate with cocaine.^{34,35} In bipolar patients with SUDs, those with PTSD have been reported to have higher rates of cocaine and amphetamine use disorders than those without PTSD.^{14–16}

The logistic regression results between anxiety disorders and SUDs from the current study support our previous findings that there are differential associations between anxiety disorders and SUDs.¹⁹ The disappearance of a significant association between panic disorder and SUDs after controlling bipolar subtype, gender, and other confounding variables in the current study supports the finding that there is panic-bipolar connections.^{36–42} Moreover, in a study of the National Epidemiological Survey on Alcohol Related Conditions (NESARC),⁴³ Compton and colleague reported that after adjusting for demographic characteristics all anxiety disorders were associated with an increased risk for drug used disorders and drug dependence. However, after adjusting for demographic variables and other psychiatric disorders, only GAD was still associated with an increased risk for drug dependence. This suggests that future studies evaluating the associations between anxiety disorders and SUDs in patients with bipolar disorder should analyze each individual anxiety disorder separately. Moreover, key variables such as bipolar subtype, gender, and other potential confounding factors should be controlled through regression modeling

The reciprocal independent associations between alcohol use disorder and drug use disorders were consistent with previous studies in non-bipolar population.^{43–45} It is not surprising that male gender is a risk factor for increased risk of any SUD, alcohol use disorder, and cocaine use disorder. Increased risk for alcoholism and drug use disorder in male than in female patients with bipolar disorder was reported previously.^{12,46} Previous studies in non-bipolar population have shown that males had a higher rate of marijuana use disorders than females.^{47–49} Therefore, a similar risk for marijuana use disorders in both genders in our study was unexpected.

The independent association of bipolar I subtype with increased risks of different SUDs is consistent with some previous studies in which higher rates of SUDs in patients with bipolar I disorder than in those with bipolar II disorder were observed.^{8,9,11} Since other potential confounding factors were controlled for in our study, it suggests that bipolar I disorder with SUDs may represent a different phenotype of bipolar disorder irrelevant to gender and/or comorbid anxiety disorders.

Interestingly, some variables related to the clinical course were associated with the increased risk for SUDs. One such variable is the age of onset of mania/hypomania. Earlier onset of first mania/hypomania was associated with increased risk for lifetime SUDs (5% increase per year) and recent marijuana dependence (12% increase per year). More importantly, the time to first mood stabilizer treatment, an indication of correct diagnosis and treatment of bipolar disorder, was negatively associated with the risk for recent SUDs (8% decrease per year). This suggests that early diagnosis and proper treatment with a mood stabilizer in bipolar disorder may reduce the risk for SUDs.

The finding that a history of physical abuse was associated with an increased risk for lifetime substance use disorder and recent marijuana dependence is consistent with previous studies in bipolar and non-bipolar population.^{50–52} A history of sexual abuse being associated with decreased risk for recent SUDs and recent alcohol dependence were unexpected although it was also associated with a trend increase in risk for lifetime cocaine dependence (Table 5). Since majority of missing data in our study was due to the lack record of a history of sexual abuse, it remains unclear if these missing cases had impacted the regression results.

Taken together, it may be advantageous for clinicians to pay more attention to drug and alcohol problem in patients with male gender, bipolar I subtype, comorbid anxiety disorder, especially GAD, and history of trauma, especially physical abuse during an initial interview and treatment. In addition, it may be important to ask substance abuse related questions when alcohol problem is present or vice versa.

Limitations

These findings should be considered in view of several methodological limitations. First, data obtained in this study was retrospective, cross-sectional, and involved four studies. Second, not all anxiety disorders were assessed, so some individuals with other anxiety disorder alone (e.g., PTSD, social phobia) could be misclassified as having no anxiety disorder. Third, as with most psychiatric cross-sectional phenomenological studies relying upon the recall of history by patients, the diagnoses and historical variables might not be accurate, although the required presence of a significant other(s) during the initial evaluation was used to minimize such potential inaccuracy. Fourth, since differences in clinical correlates between bipolar patients with RCB and those without RCB have been reported,^{36,53} therefore, our results might not be generalizable to other bipolar populations. Fifth, not adjusting for multiple comparisons may increase the chance of Type I error. Sixth, although we tried to control for potential confounding factors, factors were not forced to remain in the model could still potentially affect the final results.

Conclusion

Bipolar I disorder, male gender, a history of GAD and physical abuse, earlier onset of first mania/hypomania, and later treatment with a first mood stabilizer were associated with increased risk for one or more SUDs. This suggests that properly modifying some of these variables may prevent the development of SUDs in patients with bipolar disorder.

Acknowledgments

Supported by the Stanley Medical Research Institute, Chevy Chase, MD (Dr. Calabrese), and by grants P20 MH-66054 (Drs. Calabrese and Findling), HRSA 1 C76HF00502-01 (Dr. Calabrese), R21 MH-62650 (Dr. Calabrese), R01 MH-50165 (Dr. Calabrese), and Supplement to R01 MH-50165 (Dr. Calabrese) all from the National Institutes of Health, Bethesda, MD..

Authors thank Drs. Mark Woyshville, Melvin D. Shelton, Omar Elhaj, and Daniel J. Rapport, for their clinical work and Carla Conroy for statistical assistance.

References

1. Bauer MS, Altshuler L, Evans DR, et al. Prevalence and distinct correlates of anxiety, substance, and combined comorbidity in a multi-site public sector sample with bipolar disorder. *J Affect Disord.* 2005; 85:301–315. [PubMed: 15780700]
2. Chen YW, Dilsaver SC. Comorbidity of panic disorder in bipolar illness: evidence from the Epidemiologic Catchment Area Survey. *Am J Psychiatry.* 1995; 152:280–282. [PubMed: 7840367]
3. Chen YW, Dilsaver SC. Comorbidity for obsessive-compulsive disorder in bipolar and unipolar disorders. *Psychiatry Res.* 1995; 59:57–64. [PubMed: 8771221]
4. Grant BF, Stinson FS, Hasin DS, et al. Prevalence, correlates, and comorbidity of bipolar I disorder and Axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry.* 2005; 66:1205–1215. [PubMed: 16259532]
5. Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychological Med.* 1997; 27:1079–1089.
6. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005; 62:593–602. [PubMed: 15939837]
7. McIntyre RS, Soczynska JK, Bottas A, Bordbar K, Konarski JZ, Kennedy SH. Anxiety disorders and bipolar disorder: a review. *Bipolar Disord.* 2006; 8:665–676. [PubMed: 17156153]
8. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry.* 2007; 64:543–552. [PubMed: 17485606]
9. Merikangas KR, Herrell R, Swendsen J, Rössler W, Ajdacic-Gross V, Angst J. Specificity of bipolar spectrum conditions in the comorbidity of mood and substance use disorders. *Arch Gen Psychiatry.* 2008; 65:47–52. [PubMed: 18180428]
10. Perugi G, Toni C, Frare F, Traverso MC, Hantouche E, Akiskal HS. Obsessive-compulsive-bipolar comorbidity: a systematic exploration of clinical features and treatment outcome. *J Clin Psychiatry.* 2002; 63:1129–1134. [PubMed: 12523872]
11. 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. [PubMed: 2232018]
12. Frye MA, Altshuler LL, McElroy SL, et al. Gender differences in prevalence, risk, and clinical correlates of alcoholism comorbidity in bipolar disorder. *Am J Psychiatry.* 2003; 160:883–889. [PubMed: 12727691]
13. Goodwin RD, Stayner DA, Chinman MJ, Wu P, Tebes JK, Davidson L. The relationship between anxiety and substance use disorders among individuals with severe affective disorders. *Compr Psychiatry.* 2002; 43:245–252. [PubMed: 12107861]
14. Kolodziej ME, Griffin ML, Najavits LM, Otto MW, Greenfield SF, Weiss RD. Anxiety disorders among patients with co-occurring bipolar disorder and substance use disorder. *Drug Alcohol Depend.* 2005; 80:251–257. [PubMed: 15876498]
15. Levander E, Frye MA, McElroy S, et al. Alcoholism and anxiety in bipolar illness: differential lifetime anxiety comorbidity in bipolar I women with and without alcoholism. *J Affect Disord.* 2007; 101:211–217. [PubMed: 17254638]
16. Mitchell JD, Brown ES, Rush AJ. Comorbid disorders in patients with bipolar disorder and concomitant substance dependence. *J Affect Disord.* 2007; 102:281–287. [PubMed: 17291591]

17. Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BP). *Am J Psychiatry*. 2004; 161:2222–2229. [PubMed: 15569893]
18. Simon NM, Zalta AK, Otto MW, et al. The association of comorbid anxiety disorders with suicide attempts and suicidal ideation in outpatients with bipolar disorder. *J Psychiatr Res*. 2007; 41:255–264. [PubMed: 17052730]
19. Gao K, Tolliver BK, Kemp DE, et al. Differential interactions between comorbid anxiety and substance use disorder in rapid cycling bipolar I or II disorder. *J Affect Disord*. 2008; 110:167–173. [PubMed: 18234350]
20. Gao K, Verduin ML, Kemp DE, et al. Clinical correlates of patients with rapid cycling bipolar disorder and a recent history of substance use disorder: a subtype comparison from baseline data of 2 randomized, placebo-controlled trials. *J Clin Psychiatry*. 2008; 69:1057–1063. [PubMed: 18588360]
21. Calabrese R, Shelton MD, Rapport DJ, et al. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry*. 2005; 162:2152–2161. [PubMed: 16263857]
22. Kemp DE, Gao K, Ganocy SJ, et al. A 6-month, double-blind, maintenance trial of lithium monotherapy versus the combination of lithium and divalproex for rapid-cycling bipolar disorder and Co-occurring substance abuse or dependence. *J Clin Psychiatry*. 2009; 70:113–121. [PubMed: 19192457]
23. Gao K, Tolliver BK, Kemp DE, et al. Correlates of historical suicide attempt in rapid-cycling bipolar disorder: a cross-sectional assessment. *J Clin Psychiatry*. 2009; 70:1032–1040. [PubMed: 19653978]
24. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998; 59(Suppl 20):22–33. [PubMed: 9881538]
25. First, MB.; Spitzer, RL.; Gibbon, M., et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), Version 2. New York: New York State Psychiatric Institute, Biometrics Research; 1995.
26. Kushner MG, Sher KJ, Erickson DJ. Prospective analysis of the relation between DSM-III anxiety disorders and alcohol use disorders. *Am J Psychiatry*. 1999; 156:723–732. [PubMed: 10327905]
27. Zimmermann P, Wittchen HU, Hofler M, Pfister H, Kessler RC, Lieb R. Primary anxiety disorders and the development of subsequent alcohol use disorders: a 4-year community study of adolescents and young adults. *Psychological Med*. 2003; 33:1211–1222.
28. Bolton J, Cox B, Clara I, Sareen J. Use of alcohol and drugs to self-medicate anxiety disorders in a nationally representative sample. *J Nerv Ment Dis*. 2006; 194:818–825. [PubMed: 17102705]
29. Buckner JD, Schmidt NB, Lang AR, Small JW, Schlauch RC, Lewinsohn PM. Specificity of social anxiety disorder as a risk factor for alcohol and cannabis dependence. *J Psychiatr Res*. 2008; 42:230–239. [PubMed: 17320907]
30. Sareen J, McWilliams L, Cox B, Stein MB. Does a U-shaped relationship exist between alcohol use and DSM-III-R mood and anxiety disorders? *J Affect Disord*. 2004; 82:113–118. [PubMed: 15465583]
31. Erb S, Kayyali H, Romero K. A study of the lasting effects of cocaine pre-exposure on anxiety-like behaviors under baseline conditions and in response to central injections of corticotropin-releasing factor. *Pharmacol Biochem Behav*. 2006; 85:206–213. [PubMed: 16987545]
32. O'Brien MS, Wu LT, Anthony JC. Cocaine use and the occurrence of panic attacks in the community: a case-crossover approach. *Subst Use Misuse*. 2005; 40:285–297. [PubMed: 15776977]
33. Wood SC, Fay J, Sage JR, Anagnostaras SG. Cocaine and Pavlovian fear conditioning: dose-effect analysis. *Behav Brain Res*. 2007; 176:244–250. [PubMed: 17098299]
34. Back SE, Brady KT, Jaanimägi U, Jackson JL. Cocaine dependence and PTSD: a pilot study of symptom interplay and treatment preferences. *Addict Behav*. 2006; 31:351–354. [PubMed: 15951125]

35. Waldrop AE, Back SE, Verduin ML, Brady KT. Triggers for cocaine and alcohol use in the presence and absence of posttraumatic stress disorder. *Addict Behav.* 2007; 32:634–639. [PubMed: 16863682]
36. MacKinnon DF, Zandi PP, Gershon ES, Nurnberger JI Jr, DePaulo JR Jr. Association of rapid mood switching with panic disorder and familial panic risk in familial bipolar disorder. *Am J Psychiatry.* 2003; 160:1696–1698. [PubMed: 12944349]
37. MacKinnon DF, Zandi PP, Cooper J, et al. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. *Am J Psychiatry.* 2002; 159:30–35. [PubMed: 11772686]
38. Saunders EH, Scott LJ, McInnis MG, Burmeister M. Familiality and diagnostic patterns of subphenotypes in the National Institutes of Mental Health Bipolar sample. *Am J Med Genet B Neuropsychiatr Genet.* 2008; 147B:18–26. [PubMed: 17525972]
39. Rotondo A, Mazzanti C, Dell'Osso L, et al. Catechol O-methyltransferase, serotonin transporter, and tryptophan hydroxylase gene polymorphisms in bipolar disorder with and without comorbid panic disorder. *Am J Psychiatry.* 2002; 159:23–29. [PubMed: 11772685]
40. Simon NM, Otto MW, Fischmann D, et al. Panic disorder and bipolar disorder: anxiety sensitivity as a potential mediator of panic during manic states. *J Affect Disord.* 2005; 87:101–105. [PubMed: 15894380]
41. Goodwin RD, Hoven CW. Bipolar-panic comorbidity in the general population: prevalence and associated morbidity. *J Affect Disord.* 2002; 70:27–33. [PubMed: 12113917]
42. Birmaher B, Kennah A, Brent D, Ehmann M, Bridge J, Axelson D. Is bipolar disorder specially associated with panic disorder in youths? *J Clin Psychiatry.* 2002; 63:414–419. [PubMed: 12019666]
43. Compton WM, Thomas YF, Stinson FS, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States. *Arch Gen Psychiatry.* 2007; 64:566–576. [PubMed: 17485608]
44. Miller NS, Gold MS, Klahr AL. The diagnosis of alcohol and cannabis dependence (addiction) in cocaine dependence (addiction). *Int J Addict.* 1990; 25:735–744. [PubMed: 2272719]
45. Miller NS, Klahr AL, Gold MS, Sweeney K, Cocores JA, Sweeney DR. Cannabis diagnosis of patients receiving treatment for cocaine dependence. *J Subst Abuse.* 1990; 2:107–111. [PubMed: 2136098]
46. Kessing LV. Gender difference in the phenomenology of bipolar disorder. *Bipolar Disord.* 2004; 6:421–425. [PubMed: 15383135]
47. Karnik NS, Soller M, Redlich A, et al. Prevalence of and gender differences in psychiatric disorders among juvenile delinquents incarcerated for nine months. *Psychiatr Serv.* 2009; 60:838–841. [PubMed: 19487357]
48. Roberts RE, Roberts CR, Xing Y. Rates of DSM-IV psychiatric disorders among adolescents in a large metropolitan area. *J Psychiatr Res.* 2007; 41:959–967. [PubMed: 17107689]
49. Sussman S, Dent CW. Five-year prospective prediction of marijuana use cessation of youth at continuation high schools. *Addict Behav.* 2004; 29:1237–1243. [PubMed: 15236829]
50. Hyman SM, Garcia M, Sinha R. Gender specific associations between types of childhood maltreatment and the onset, escalation, and severity of substance use in cocaine dependent adults. *Am J Drug Alcohol Abuse.* 2006; 32:655–664. [PubMed: 17127554]
51. Goldstein BI, Strober MA, Birmaher B, et al. Substance use disorders among adolescents with bipolar spectrum disorders. *Bipolar Disord.* 2008; 10:469–478. [PubMed: 18452443]
52. Post RM, Leverich GS, Xing G, Weiss RB. Developmental vulnerabilities to the onset and course of bipolar disorder. *Dev Psychopathol.* 2001; 13:581–598. [PubMed: 11523849]
53. Kupka RW, Luckenbaugh DA, Post RM, et al. Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. *Am J Psychiatry.* 2005; 162:1273–1280. [PubMed: 15994709]

Table 1

Demographics and Clinical Correlates of Patients with Rapid Cycling Bipolar Disorder with or without Comorbid Anxiety Disorder

	With AD (n=261)			Without AD (n=303)			w AD versus w/o AD	
	Mean	SD		Mean	SD			P
Age (years)	35.5	10.1		37.3	10.7		not applicable	0.0440
Episodes in last 12 months	12.8	7.0		10.8	7.1		not applicable	0.0120
	N	%		N	%		OR (Wald 95% CI)	Pearson's P
Gender								
- Male	119	45.6		147	48.5		0.9 (0.64–1.24)	0.4883
- Female	142	54.4		156	51.5			
Bipolar Subtypes								
- Bipolar I disorder	174	66.7		146	48.2		2.2 (1.53–3.03)	< 0.0001
- Bipolar II disorder	87	33.3		157	51.8			
Lifetime Substance Use Disorder								
- Any	174	66.7		201	66.3		1.0 (0.72–1.44)	0.9340
- Abuse								
- Alcohol	40	15.3		89	29.4		0.4 (0.29–0.66)	< 0.0001
- Marijuana	51	19.5		84	27.7		0.6 (0.43–0.94)	0.0231
- Cocaine	35	13.4		35	11.6		1.2 (0.72–1.96)	0.5044
- Other Drugs*	35	13.4		51	16.8		0.8 (0.48–1.22)	0.2597
- Dependence								
- Alcohol	115	44.1		83	27.4		2.1 (1.47–2.97)	< 0.0001
- Marijuana	46	17.6		18	5.9		3.4 (1.91–6.01)	< 0.0001
- Cocaine	42	16.1		46	15.2		1.1 (0.68–1.69)	0.7663
- Other Drugs*	16	6.1		7	2.3		2.8 (1.12–6.82)	0.0221
Recent Substance Use Disorder								
- Any	96	36.8		84	27.72		1.5 (1.06–2.17)	0.0214
- Abuse								
- Alcohol	14	5.4		32	10.56		0.5 (0.25–0.92)	0.0205
- Marijuana	17	6.5		32	10.56		0.6 (0.32–1.08)	0.0888

	With AD (n=261)		Without AD (n=303)		w AD versus w/o AD	
	Mean	SD	Mean	SD		P
- Cocaine	10	3.8	8	2.64	1.5 (0.57–3.78)	0.4223
- Dependence						
- Alcohol	60	23.0	37	12.21	2.1 (1.37–3.36)	0.0007
- Marijuana	19	7.3	9	2.97	2.6 (1.14–5.77)	0.0188
- Cocaine	16	6.1	17	5.61	1.1 (0.54–2.22)	0.7932
Previous History						
- Psychois	124	48.1	120	39.6	1.4 (1.01–1.97)	0.0440
- Abuse						
- Verbal	111	46.1	133	52.6	0.8 (0.54–1.10)	0.1479
- Physical	80	33.2	86	33.9	1.0 (0.67–1.41)	0.8759
- Sexual	62	25.7	64	25.6	1.0 (0.67–1.51)	0.9745

* Other drugs included stimulants, sedatives, opiate, and hallucinogens.

Abbreviation: AD, anxiety disorder; N, Number; ns, not significant; OR, odds ratio; P, p value; SD, standard deviation; w, with; w/o without.

Table 2
Predictors of the Probability for a Lifetime or Recent Substance Use Disorder in Rapid Cycling Bipolar Disorder

Variables	Lifetime Substance Use Disorder				Recent Substance Use Disorder			
	Estimate	OR	95% CI	P value	Estimate	OR	95% CI	P value
Bipolar I disorder	0.21	1.23	0.719–2.111	0.4473	1.29	3.64	2.036–6.517	<.0001
Being male	0.71	2.03	1.303–3.165	0.0018	0.20	1.22	0.715–2.088	0.4626
History of generalized anxiety disorder	0.85	2.34	1.119–4.897	0.0240	–0.60	0.55	0.203–1.493	0.2414
History of obsessive compulsive disorder	–0.73	0.48	0.204–1.128	0.0921	0.16	1.18	0.380–3.652	0.7763
History of panic disorder	0.24	1.27	0.651–2.476	0.4830	–0.49	0.61	0.287–1.301	0.2016
Age onset of first mania/hypomania	–0.05	0.95	0.926–0.984	0.0027	n/a	n/a	n/a	n/a
Age at study entry	n/a	n/a	n/a	n/a	0.06	0.95	0.893–1.000	0.0495
History of any anxiety disorder	–0.78	0.46	0.188–1.127	0.0893	1.23	3.42	1.055–11.101	0.0405
History of physical abuse	0.54	1.71	1.067–2.735	0.0257	0.69	1.99	1.120–3.540	0.0191
History of psychosis	0.64	1.90	1.106–3.264	0.0202	n/a	n/a	n/a	n/a
History of sexual abuse	n/a	n/a	n/a	n/a	–0.94	0.39	0.199–0.766	0.0063
History of alcohol use disorder	n/a	n/a	n/a	n/a	1.97	7.15	3.662–13.954	<.0001
History of drug use disorder	n/a	n/a	n/a	n/a	1.50	4.47	2.469–8.075	<.0001
Age of first mood stabilizer treatment	n/a	n/a	n/a	n/a	0.07	1.08	1.018–1.137	0.0095
$\chi^2 = 57.2935$, df = 9, p-value = <.0001				$\chi^2 = 174.9722$, df = 12, p-value = <.0001				

Abbreviation: CI, confidence interval; OR, odds ratio.

Table 3
Predictors of the Probability for a Lifetime or Recent Alcohol Dependence in Rapid Cycling Bipolar Disorder

Variables	Lifetime Alcohol Dependence				Recent Alcohol Dependence			
	Estimate	OR	95% CI	P value	Estimate	OR	95% CI	P value
Bipolar I disorder	0.63	1.88	1.188–2.973	0.0070	1.15	3.17	1.672–6.015	0.0004
Being male	0.64	1.89	1.214–2.948	0.0049	0.30	1.35	0.760–2.410	0.3048
History of generalized anxiety disorder	0.55	1.73	1.054–2.850	0.0301	–0.84	0.43	0.176–1.051	0.0641
History of obsessive compulsive disorder	0.45	1.57	0.663–3.732	0.3043	0.16	1.18	0.399–3.469	0.7682
History of panic disorder	0.36	1.44	0.853–2.418	0.1727	–0.22	0.81	0.388–1.670	0.5609
Age at study entry	0.02	1.02	1.002–1.045	0.0316	n/a	n/a	n/a	n/a
History of any anxiety disorder	n/a	n/a	n/a	n/a	1.58	4.88	1.625–14.634	0.0047
History of sexual abuse	n/a	n/a	n/a	n/a	–0.71	0.49	0.243–1.001	0.0503
History of drug use disorder	1.21	3.36	2.138–5.286	<.0001	1.09	2.97	1.662–5.311	0.0002
Age of first mood stabilizer treatment	n/a	n/a	n/a	n/a	0.02	1.03	0.999–1.051	0.0577

$\chi^2 = 78.1184$, df = 7, p-value = <.0001 $\chi^2 = 52.8552$, df = 9, p-value = <.0001

Abbreviation: CI, confidence interval; OR, odds ratio.

Table 4
Predictors of the Probability for a Lifetime or Recent Marijuana Dependence in Rapid Cycling Bipolar Disorder

Variables	Lifetime Marijuana Dependence				Recent Marijuana Dependence			
	Estimate	OR	95% CI	P value	Estimate	OR	95% CI	P value
Bipolar I disorder	0.89	2.43	1.104–5.327	0.0274	1.56	4.76	1.307–17.310	0.0180
Being male	0.37	1.44	0.758–2.752	0.2637	0.24	1.27	0.518–3.129	0.5995
History of generalized anxiety disorder	1.21	3.36	1.646–6.856	0.0009	1.19	3.28	1.214–8.863	0.0191
History of obsessive compulsive disorder	−1.81	0.16	0.019–1.385	0.0968	−0.76	0.47	0.057–3.823	0.4790
History of panic disorder	0.14	1.15	0.567–2.335	0.6978	−0.44	0.65	0.241–1.726	0.3823
Age at study entry	−0.07	0.94	0.904–0.969	0.0002	Table 4	0.94	0.895–0.988	0.0148
History of cocaine dependence	1.58	4.87	2.321–10.216	<.0001	n/a	n/a	n/a	n/a
History of cocaine abuse	0.87	2.39	1.023–5.578	0.0442	n/a	n/a	n/a	n/a
Age onset of first mania/hypomania	n/a	n/a	n/a	n/a	−0.13	0.88	0.803–0.968	0.0079
Age onset of depression	n/a	n/a	n/a	n/a	0.11	1.12	1.017–1.222	0.0210
History of physical abuse	n/a	n/a	n/a	n/a	1.24	3.47	1.385–8.673	0.0079
				$\chi^2 = 77.7694$, df = 8, p-value = <.0001				
				$\chi^2 = 40.4425$, df = 9, p-value = <.0001				

Table 5
Predictors of the Probability for a Lifetime or Recent Cocaine Dependence in Rapid Cycling Bipolar Disorder

Variables	Lifetime Cocaine Dependence				Recent Cocaine Dependence			
	Estimate	OR	95% CI	P value	Estimate	OR	95% CI	P value
Bipolar I disorder	1.20	3.33	1.603–6.893	0.0013	0.53	1.71	0.686–4.251	0.2506
Being male	0.37	1.45	0.766–2.744	0.2542	0.84	2.31	0.950–5.631	0.0648
History of generalized anxiety disorder	0.01	1.01	0.494–2.054	0.9845	0.40	1.49	0.573–3.873	0.4139
History of obsessive compulsive disorder	0.19	1.21	0.307–4.762	0.787	−0.34	0.71	0.086–5.927	0.7547
History of panic disorder	−0.38	0.68	0.326–1.431	0.3131	−0.63	0.53	0.171–1.658	0.2763
Number of mania/hypomania in last 12 month	0.08	1.09	1.005–1.173	0.038	n/a	n/a	n/a	n/a
History of marijuana dependence	2.03	7.63	3.468–16.781	< 0.001	n/a	n/a	n/a	n/a
History of marijuana abuse	1.82	6.14	3.052–12.358	< 0.001	0.78	2.19	0.931–5.131	0.0727
History of sexual abuse	0.64	1.89	0.957–3.729	0.067	n/a	n/a	n/a	n/a
History of alcohol abuse	n/a	n/a	n/a	n/a	0.89	2.44	1.037–5.749	0.0410
$\chi^2 = 76.9775$, df = 9, p-value = <.0001					$\chi^2 = 17.8818$, df = 7, p-value = 0.0125			

Abbreviation: CI, confidence interval; OR, odds ratio.