The Relationship Between Smoking and Suicidal Behavior, Comorbidity, and Course of Illness in Bipolar Disorder

Michael J. Ostacher, M.D., M.P.H.; Andrew A. Nierenberg, M.D.; Roy H. Perlis, M.D.; Polina Eidelman, B.A.; David J. Borrelli, M.D.; Tanya B. Tran, B.A.; Gianna Marzilli Ericson, B.A.; Roger D. Weiss, M.D.; and Gary S. Sachs, M.D.

Objectives: The rate of smoking in people with bipolar disorder is much greater than in the general population, but the implications of smoking for the course of bipolar disorder have not been well studied. The purpose of this retrospective study was to examine the relationship between smoking, severity of bipolar disorder, suicidal behavior, and psychiatric and substance use disorder comorbidity.

Method: We evaluated 399 outpatients with bipolar disorder who were treated in a bipolar specialty clinic from December 1999 to October 2004. Diagnosis, mood state, course of illness, functioning, and psychiatric comorbidities were assessed using the Affective Disorders Evaluation and the Mini-International Neuropsychiatric Interview.

Results: Of the 399 patients evaluated, 155 (38.8%) had a history of daily smoking. Having ever smoked was associated with earlier age at onset of first depressive or manic episode, lower Global Assessment of Functioning scores, higher Clinical Global Impressions-Bipolar Disorder scale scores, lifetime history of a suicide attempt (47% for smokers vs. 25% for those who had never smoked), and lifetime comorbid disorders: anxiety disorders, alcohol abuse and dependence, and substance abuse and dependence. In a logistic regression model including these factors, suicide attempts and substance dependence were significantly associated with smoking in patients with bipolar disorder.

Conclusions: Bipolar patients with lifetime smoking were more likely to have earlier age at onset of mood disorder, greater severity of symptoms, poorer functioning, history of a suicide attempt, and a lifetime history of comorbid anxiety and substance use disorders. Smoking may be independently associated with suicidal behavior in bipolar disorder.

(J Clin Psychiatry 2006;67:1907–1911)

Received March 31, 2006; accepted May 24, 2006. From Massachusetts General Hospital Bipolar Clinic and Research Program, Boston (Drs. Ostacher, Nierenberg, Perlis, Borrelli, and Sachs and Mss. Eidelman, Tran, and Ericson); McLean Hospital, Belmont (Dr. Weiss); and the Department of Psychiatry, Harvard Medical School, Boston (Drs. Ostacher, Nierenberg, Perlis, Borrelli, Weiss, and Sachs), Mass.

Dr. Weiss was supported by National Institute on Drug Abuse grants R01 DA00326 and R01 DA15968, and Dr. Borrelli was supported by an unrestricted educational grant from Janssen Pharmaceuticals.

Financial disclosure appears at the end of this article.

Corresponding author and reprints: Michael D. Ostacher, M.D., M.P.H., Massachusetts General Hospital, Bipolar Clinic and Research Program, 50 Staniford St., Suite 580, Boston, MA 02114 (e-mail: mostacher@partners.org).

Nicotine dependence is disproportionately prevalent in people with mental illness, including those with bipolar disorder.[1–3] Remarkably, Grant et al.[3] have found that people with mental illness and comorbid nicotine dependence smoked 34.2% of the cigarettes sold in the United States in 2001–2002, although they comprise only 7.1% of the population. The prevalence of nicotine dependence in bipolar disorder is markedly elevated; 35.3% (odds ratio [OR] = 3.9) of those with bipolar I disorder and 33.4% (OR = 3.5) of those with bipolar II disorder met criteria for nicotine dependence in the prior 12 months, compared with only 12.8% in the general population.[3] This elevated rate of smoking may contribute to the elevated risk of death from natural causes in bipolar disorder compared with the general population.[4]

Cigarette smoking may be associated with poor course of illness and more suicidal behavior in bipolar disorder. In a cohort of 65 patients with bipolar disorder and 243 patients with major depressive disorder, Oquendo et al.[5] found that the most robust predictors of suicidal behavior following a major depressive episode were smoking, severity of depression, and having made a prior suicide attempt. Smoking has been associated with a history of psychosis in bipolar disorder[6]; moreover, the severity of psychosis is correlated with greater severity of smoking.

Oquendo et al.,[5] Mann et al.,[7] and Dumais et al.[8] have suggested that there may be an aggression/impulsivity factor that predisposes certain patients with bipolar disorder to suicidal behavior, substance use disorders, and smoking. While smoking has been associated with suicide

attempts in patients with mood disorders, the strong association between smoking and other comorbidities (e.g., substance use disorders and anxiety disorders) suggests that smoking may not be an independent risk factor for suicide and other impulsive behavior.[7] It is unclear if the association between smoking and suicidal behavior is due to a factor that is independent from mood symptoms, substance use disorder and anxiety disorder comorbidity, or illness severity. Determining whether smoking is a phenotypic marker for more impulsive behavior in bipolar disorder would inform clinical decision making and risk management and may point to an endophenotype for genetic study in families of smokers with bipolar disorder.

By examining the characteristics of a relatively large sample of outpatients with bipolar disorder, we intended to explore the relationship between smoking and illness severity, psychiatric comorbidity, and suicidal behavior. Our primary hypothesis was that smoking would be associated with increased suicidality in these subjects. Secondary hypotheses were that smoking would be associated with earlier onset of illness, more severe symptoms, worse functioning, and increased psychiatric and substance use disorder comorbidity.

METHOD

Data were collected from an electronic database for consecutive patients admitted to the Massachusetts General Hospital Bipolar Clinic and Research Program between December 1, 1999, and October 31, 2004, for whom data on smoking history were available. Informed consent was obtained prior to data collection, and the Partners Healthcare System Institutional Review Board approved the study. Data were collected from the Affective Disorders Evaluation (ADE)[9] and the Mini-International Neuropsychiatric Interview (MINI Plus),[10] both semistructured interviews completed by clinicians with high interrater reliability, as shown by Sachs.[11] Information collected from the ADE included baseline sociodemographic characteristics, medications, a Structured Clinical Interview for DSM (SCID)-based interview for mood disorders, symptom ratings for current depressive and manic symptoms, Global Assessment of Functioning (GAF)[12] scores, Clinical Global Impressions-Bipolar Disorder scale (CGI-BD)[13] scores, age at onset of mood disorder, current and past smoking history, and prior suicide attempts. Smoking status was obtained by self report; subjects who reported regularly smoking 1 or more cigarettes a day at entry into the study or who reported regularly smoking 1 or more cigarettes a day in the past were considered smokers. Oral tobacco (snuff) users were not included in the analyses. Information collected from the MINI included lifetime histories of comorbid psychiatric and substance use disorders.

Analysis utilized descriptive parametric and nonparametric statistics including χ^2 and Mantel-Haenszel common OR estimates for the primary outcome measures and t tests for continuous variables such as age at onset, CGI scores, and GAF scores, using the SPSS statistical program (version 13.0 for Windows, SPSS Inc., Chicago, Ill.). A multiple logistic regression model, using history of smoking as the dependent variable and the factors that were statistically significant in a univariate analysis as independent variables, was performed to control for possible confounding factors.

RESULTS

Three hundred ninety-nine bipolar patients were assessed, of whom 38.8% had a history of daily smoking. Those with a lifetime history of smoking were similar in age, sex, and marital status compared with those who had never smoked. There was a trend ($p = .055$) for smokers to be unemployed or unable to work (Table 1).

Having ever smoked was associated with earlier age at onset of first depressive episode (15.7 ± 7.7 vs. 18.2 ± 8.3 years, $p = .004$), earlier age at onset of first manic episode (19.7 ± 9.5 vs. 22.4 ± 9.8 years, $p = .013$), lower GAF scores (56.1 ± 9.8 vs. 59.1 ± 9.6, $p = .003$), higher CGI-BP scores (3.1 vs. 2.8, $p = .015$), a history of a comorbid anxiety disorder (68% vs. 53%, OR = 1.82, 95% CI = 1.09 to 3.06; $p = .023$), a history of alcohol dependence (46.7% vs. 20.6%, OR = 3.38, 95% CI = 2.15 to 5.29; $p < .001$), a history of alcohol abuse (40.0% vs. 20.6%, OR = 2.57, 95% CI = 1.63 to 4.05; $p < .001$), a history of substance dependence (33.3% vs. 12.7%, OR = 3.45, 95% CI = 2.07 to 5.76; $p < .001$), a history of substance abuse (24.0% vs. 14.8%, OR = 1.82, 95% CI = 1.09 to 3.06; $p = .023$), and lifetime history of a suicide attempt (47% vs. 25%, OR = 2.74, 95% CI = 1.77 to 4.23; $p < .001$).

In a logistic regression model with history of smoking as the dependent variable and age at onset of depression, age at onset of mania, having made a suicide attempt, GAF scores, CGI-BP scores, and a lifetime history of an anxiety disorder, alcohol dependence, alcohol abuse, substance dependence, and substance abuse as covariates, having made a suicide attempt (OR = 2.25, 95% CI = 1.31 to 3.86; $p = .003$) and having a history of substance dependence (OR = 2.30, 95% CI = 1.14 to 4.65; $p = .02$) remained significantly associated with smoking in patients with bipolar disorder (Table 2).

DISCUSSION

A history of smoking in patients with bipolar disorder is associated with a more severe course of illness and increased anxiety, alcohol use, and substance use disorder comorbidity. Notably, smokers with bipolar disorder have a worse course of illness that includes earlier age at onset of first mood episode, poorer functioning, more severe symptoms, and having made a suicide attempt. These data

Table 1. Sociodemographic Characteristics of Bipolar Patients Who Have Never Smoked in Their Lifetime and Bipolar Patients Who Have Ever Smoked in Their Lifetime*

Characteristic	Bipolar Patients Who Have Ever Smoked (N = 155)	Bipolar Patients Who Have Never Smoked (N = 244)	Analysis		
			Test Result	df	p
Age, y			t = 0.242	390	.809
Mean (SD)	38.46 (11.59)	38.71 (12.54)			
Median (range)	38 (18–72)	37 (16–74)			
Sex			$\chi^2 = 0.051$	1	.822
Male	70 (45.2)	113 (46.3)			
Female	85 (54.8)	131 (53.7)			
Marital status†			$\chi^2 = 0.317$	1	.573
Never married	72 (62.1)	102 (65.4)			
Ever married or living as married	44 (37.9)	54 (34.6)			
Race†			$\chi^2 = 3.1302$	1	.077
White	140 (92.7)	232 (96.7)			
Nonwhite	11 (7.3)	8 (3.3)			
Bipolar subtype			$\chi^2 = 1.571$	3	.666
Bipolar I disorder	99 (63.9)	160 (65.6)			
Bipolar II disorder	43 (27.7)	60 (24.6)			
Bipolar NOS	9 (5.8)	20 (8.2)			
Other‡	4 (2.6)	4 (1.6)			
Employment status†			$\chi^2 = 3.691$	1	.055
Full-time, part-time, homemaker, retired	73 (51.8)	143 (61.9)			
Disabled, leave of absence, unemployed	68 (48.2)	88 (38.1)			

*Data shown as N (%) unless otherwise noted.
†Data missing in ≤ 24 subjects with bipolar disorder.
‡Other bipolar subtype = schizoaffective bipolar, cyclothymia, psychotic disorder.
Abbreviation: NOS = not otherwise specified.

Table 2. Logistic Regression for Association Between Smoking and Markers of Illness Severity

Covariate	B	SE[a]	Wald	df	Level of Significance	Odds Ratio	95% CI	
							Lower	Upper
Age at onset of depression	–0.016	0.020	0.656	1	.418	0.984	0.964	1.023
Age at onset of mania	–0.006	0.016	0.125	1	.723	0.994	0.964	1.026
Suicide attempt	0.812	0.275	8.715	1	.003	2.253	1.314	3.862
GAF score, current month	–0.003	0.020	0.017	1	.897	0.997	0.959	1.037
CGI-BP score	0.118	0.138	0.730	1	.393	1.125	0.858	1.476
Any lifetime anxiety disorder	0.100	0.283	0.126	1	.723	1.106	0.635	1.927
Lifetime alcohol dependence	0.505	0.311	2.630	1	.105	1.656	0.900	3.048
Lifetime alcohol abuse	0.191	0.318	0.362	1	.547	1.211	0.649	2.258
Lifetime substance dependence	0.835	0.358	5.428	1	.020	2.304	1.142	4.649
Lifetime substance abuse	0.083	0.375	0.049	1	.826	1.086	0.521	2.266

[a]Standard error for the odds ratio.
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar Disorder scale, GAF = Global Assessment of Functioning scale.

add to the accumulating evidence of an association between smoking and greater psychiatric morbidity and mortality.[5]

Increased suicidality in smokers in this bipolar cohort is consistent with a previous study by Oquendo et al.[5] Since the association between suicidality and psychiatric comorbidity (such as anxiety disorders and substance use disorder) has previously been reported by Simon et al.[14] and Dumais et al.,[8] a regression model was used to determine which comorbidities and other clinical factors would remain associated with smoking in bipolar disorder. Consistent with our hypothesis, the association between smoking and suicide attempts remained significant when factors found in univariate analyses to be significantly associated with smoking were controlled for in a logistic regression model. Only substance dependence also remained significantly associated with smoking in this model, strongly suggesting that a history of a suicide attempt is independently associated with a history of smoking.

Interestingly, only the association between substance dependence (but not alcohol abuse or dependence or substance abuse) and smoking remained significant in this model. It is unclear why the association between alcohol

dependence was no longer significant, although a larger sample may be useful in further exploring whether this factor contributes to the model. The finding that the association between substance and alcohol abuse did not contribute to the association in the regression model is perhaps not surprising, as less severe substance use disorders may represent less impulsive and disordered behavior compared with that found in dependence syndromes.

Because smoking was associated with suicide attempts after controlling for comorbid conditions and illness severity, this study gives further evidence that there is a factor independent of mood, such as the impulsivity/aggression factor postulated to be associated with suicide, that is more common in smokers. Whether this factor leads to the initiation of smoking in patients with bipolar disorder, or, instead, is a result of cigarette use itself cannot be answered by this study. The independent association between smoking and suicidal behavior may point to smoking as an area for further exploration as an endophenotype associated with impulsive behavior in bipolar families.

There are several limitations to this study. The data obtained were cross-sectional and retrospective. Another limitation of this study is that we do not know whether suicide attempts were associated with attempts to quit smoking in these patients. One hypothesis that may explain part of the increased risk of suicide in smokers is that recently abstinent smokers with a history of major depression are prone to relapse to depression; Balfour and Ridley[15] suggest a model in which continued smoking is protective against depression. We also were unable to separately examine the group of former smokers with regard to these associations, as the number of former smokers in this study is small. It does appear, however, that sustained smoking cessation is infrequent in patients with bipolar disorder; only 18% of ever smokers in this group with bipolar disorder were not smoking at entry into this study, while King et al.[16] reported that approximately half of ever smokers in the general population have quit.

Another limitation of this study is that we used self-reports of nicotine use rather than a formal diagnosis of nicotine dependence. Several studies, including that by Schmitz et al.,[17] have differentiated nicotine use from dependence and found that dependent individuals had higher rates of disability and psychiatric comorbidity than those who casually used nicotine. Because we included those who were past but not current smokers and those whose smoking may not have met the severity necessary for a diagnosis of nicotine dependence, it is likely that we underestimated the association between smoking and suicide attempts. Also, because we do not know the age at onset of smoking, we do not know whether smoking predates the development of mood disorder preferentially in one group or another and thus cannot infer that nicotine use in itself increases the risk for the development of bipolar disorder. We do not have data on comorbid personality disorders and cannot know whether they account for the elevation of suicide attempts in the smoking group, as smoking is increased in bipolar patients with personality disorders as suggested by Waxmonsky et al.[18]

This study suggests a strong association between smoking, substance dependence, and suicide attempts in patients with bipolar disorder. No large studies of treatments for nicotine dependence and few large studies of treatments for substance use disorders have been conducted in patients with bipolar disorder. It will be important to determine whether interventions targeting nicotine and substance use comorbidities will have an impact on clinical course and overall mortality in this population. The relationship between smoking, impulsive behavior, and mood should be further explored.

Financial disclosure: Dr. Ostacher has received honoraria from AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, Pfizer, and Concordant Rater Systems; has received research funding from Pfizer; and has been a consultant to HealthGate Data Corp. Dr. Nierenberg has been a consultant for Bristol-Myers Squibb, Genaissance, GlaxoSmithKline, Innapharma, Janssen, Eli Lilly, Novartis, Pfizer, Sepracor, Shire, and Somerset; has received grant support from Bristol-Myers Squibb, Cederroth, Cyberonics, Forest, GlaxoSmithKline, Janssen, Lichtwer Pharma, Eli Lilly, the National Alliance for Research on Schizophrenia and Depression, the National Institute of Mental Health, Pfizer, the Stanley Foundation, and Wyeth-Ayerst; and has received honoraria from Bristol-Myers Squibb, Cyberonics, Forest, GlaxoSmithKline, Eli Lilly, and Wyeth-Ayerst. Dr. Perlis has received honoraria, speakers' fees, or consulting fees from GlaxoSmithKline, Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Elan/Eisai, Pfizer, and Shire. Dr. Weiss is on the speakers' bureau for Abbott and on the board of advisors for Alkermes. Dr. Sachs is a consultant to Abbott, GlaxoSmithKline, Shire, Janssen, Eli Lilly, Bristol-Myers Squibb, Novartis, Sanofi, and AstraZeneca; has received grant/research support from Janssen and Wyeth; and has received honoraria from Abbott, GlaxoSmithKline, Janssen, Eli Lilly, Wyeth, Bristol-Myers Squibb, Solvay, Novartis, Sanofi, AstraZeneca, and Pfizer. Dr. Borrelli and Mss. Eidelman, Tran, and Ericson report no additional financial or other relationships relevant to the subject of this article.

REFERENCES

1. de Leon J, Diaz FJ, Rogers T, et al. Initiation of daily smoking and nicotine dependence in schizophrenia and mood disorders. Schizophr Res 2002;56:47–54
2. Gonzalez-Pinto A, Gutierrez M, Ezcurra J, et al. Tobacco smoking and bipolar disorder. J Clin Psychiatry 1998;59:225–228
3. Grant BF, Hasin DS, Chou SP, et al. Nicotine dependence and psychiatric disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 2004;61:1107–1115
4. Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001;58:844–850
5. Oquendo MA, Galfalvy H, Russo S, et al. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. Am J Psychiatry 2004;161:1433–1441
6. Corvin A, O'Mahony E, O'Regan M, et al. Cigarette smoking and psychotic symptoms in bipolar affective disorder. Br J Psychiatry 2001;179:35–38
7. Mann JJ, Waternaux C, Haas GL, et al. Toward a clinical model of suicidal behavior in psychiatric patients. Am J Psychiatry

1999;156:181–189
8. Dumais A, Lesage AD, Alda M, et al. Risk factors for suicide completion in major depression: a case-control study of impulsive and aggressive behaviors in men. Am J Psychiatry 2005;162:2116–2124
9. Sachs G, Thase ME, Otto MW, et al. Rationale, design, and methods of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2003;53:1028–1042
10. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33; quiz 34–57
11. Sachs GS. Use of clonazepam for bipolar affective disorder. J Clin Psychiatry 1990;51(5, suppl):31–34
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994:32
13. Spearing MK, Post RM, Leverich GS, et al.Modifications of the clinical global impressions (CGI) scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997;73:159–171
14. Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2004;161:2222–2229
15. Balfour DJ, Ridley DL. The effects of nicotine on neural pathways implicated in depression: a factor in nicotine addiction? Pharmacol Biochem Behav 2000;66:79–85
16. King G, Polednak A, Bendel RB, et al. Disparities in smoking cessation between African Americans and whites: 1990–2000. Am J Public Health 2004;94:1965–1971
17. Schmitz N, Kruse J, Kugler J. Disabilities, quality of life, and mental disorders associated with smoking and nicotine dependence. Am J Psychiatry 2003;160:1670–1676
18. Waxmonsky JA, Thomas MR, Miklowitz DJ, et al. Prevalence and correlates of tobacco use in bipolar disorder: data from the first 2000 participants in the Systematic Treatment Enhancement Program. Gen Hosp Psychiatry 2005;27:321–328

