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Cigarette smoking is associated with suicidality in bipolar disorder

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Abstract

Objectives—Cigarette smoking in individuals with bipolar disorder has been associated with suicidal behavior, although the precise relationship between the two remains unclear.

Methods—In this prospective observational study of 116 individuals with bipolar disorder, we examined the association between smoking and suicidality as measured by Linehan’s Suicide Behaviors Questionnaire (SBQ) and prospective suicide attempts over a nine-month period. Impulsivity was measured by the Barratt Impulsiveness Scale.

Results—Smoking was associated with higher baseline SBQ scores in univariate and adjusted analyses, but was not significant after statistical adjustment for impulsivity in a regression model. A higher proportion of smokers at baseline made a suicide attempt during the follow-up period (5/31, 16.1%) compared to nonsmokers (3/85, 3.5%); $p = 0.031$, odds ratio = 5.25 (95% confidence interval: 1.2–23.5). Smoking at baseline also significantly predicted higher SBQ score at nine months.

Conclusions—In this study, current cigarette smoking was a predictor of current and nine-month suicidal ideation and behavior in bipolar disorder, and it is likely that impulsivity accounts for some of this

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Disclosures

In the last five years, MJO has received consulting fees/honoraria from Concordant Rater Systems, AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Co., Forest, GlaxoSmithKline, Massachusetts General Hospital Psychiatry Academy, Janssen, and Pfizer. In the last five years, RHP has received consulting fees/honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Co., GlaxoSmithKline, Pfizer, and Proteus; has received speakers fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Co., GlaxoSmithKline, and Pfizer; and has been a stockholder in Concordant Rater Systems, LLC. In the past three years, AAN has received research support from Cyberonics, Cederroth, Ortho-McNeil-Janssen, Pfizer, Pam Labs, and Shire; consulted to and served on advisory boards of Abbott Laboratories, Appliance Computing, Inc., Brain Cells, Inc, Bristol-Myers Squibb, EpiQ, Pam Labs, PGX Health, Forest, Eli Lilly & Co, GlaxoSmithKline, Janssen, Jazz, Merck, Novartis, Pfizer, Schering-Plough, Sepracor, Shire, Somerset, Takeda, and Targacept; has received honoraria from the MGH Psychiatry Academy [supported in 2008 through Independent Medical Education (IME) grants from AstraZeneca, Eli Lilly & Co., and Janssen]; and has owned stock options in Appliance Computing, Inc. NMS has received research grants from AstraZeneca, Bristol-Myers Squibb, Cephalon, Forest, GlaxoSmithKline, Janssen, Eli Lilly & Co., NARSAD, NIMH, Pfizer, UCB-Pharma, and Sepracor; has served on advisory boards or provided consultation for the American Foundation for Suicide Prevention, Paramount Biosciences, Pfizer, Sepracor, and Solvay; and has served as speaker/CME presenter for AstraZeneca, Forest, MGH Psychiatry Academy, Janssen, Eli Lilly & Co., Pfizer, and UCB-Pharma. RTL, HGL, SJM, and GSS have no conflicts of interest related to this work.

Keywords

bipolar disorder; impulsivity; nicotine; smoking; substance abuse; suicidality

Bipolar patients have markedly elevated rates of nicotine dependence (1,2). Compared to only 12.8% in the general population, 35.3% of those with bipolar I disorder [odds ratio (OR) = 3.9] and 33.4% of those with bipolar II disorder (OR = 3.5) met criteria for nicotine dependence in the prior 12 months (2). Beyond the adverse health implications of smoking, bipolar patients who smoke are at higher risk of suicidal behavior and suicide attempts, independent of substance abuse and anxiety disorder comorbidity (3). Along with severity of depression and having made a prior suicide attempt, smoking was a robust predictor of suicidal behavior following a major depressive episode in bipolar disorder, even after controlling for other factors (4) and regardless of gender (5). Additionally, a study of adolescents with bipolar disorder found that cigarette smoking was independently associated with suicide attempts and substance use disorders (6,7).

It is unclear why smokers with bipolar disorder are more likely to make suicide attempts. Some have suggested that an aggression/impulsivity factor may predispose certain individuals with bipolar disorder to suicidal behavior, substance use disorders, and smoking (4,8,9). In a prospective study, hostility predicted suicide attempts in individuals with bipolar disorder, although the relationship between hostility and smoking was not examined (10).

In this prospective, longitudinal study of suicidal ideation and behavior in a clinical sample of patients with bipolar disorder, we examined current cigarette smoking using a well-validated measure of suicidal ideation and behaviors at baseline and prospectively at nine-month follow-up, and employed a validated assessment of impulsivity. We hypothesized that smoking would be a significant predictor of suicidality at baseline and at nine-month follow-up.

Methods

Subjects and clinical assessments

This study was designed as an ancillary project to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a National Institute of Mental Health (NIMH) funded observational study. Demographic and diagnostic data were provided from the STEP-BD database. Details of the methodology of STEP-BD and this ancillary study have been published elsewhere (11,12), and are thus briefly described here. STEP-BD enrolled subjects in usual clinical care who were willing to undergo longitudinal clinical assessments (13). Clinician assessments with the Mini International Neuropsychiatric Interview [MINI Plus Version 5.0 (14)], adapted to assess lifetime anxiety disorders, occurred every 12 months. Current clinical bipolar status based on the presence or absence of DSM-IV-based criteria was assessed at every clinical visit. Patients achieving relative euthymia (< 2 moderate symptoms of depression or mania/hypomania) for at least a week were assigned a status of recovering or recovered, depending on whether this status was sustained for at least eight weeks. Current bipolar status was assessed at the most recent clinical visit, a mean \pm SD of 1.6 ± 2.5 months prior to questionnaire completion.

All active participants in the Massachusetts General Hospital (MGH) site of STEP-BD as of September 23, 2003 (n = 258) were mailed the study questionnaire packet on October 23, 2003. A cover letter requested that they complete the questionnaires for a study examining “the relationship between anxiety symptoms, bipolar disorder and suicidality.” Study

procedures were approved by the MGH Institutional Review Board and were in accordance with the Helsinki Declaration of 1975. Patients who returned the questionnaire packet were then sent a follow-up packet nine months later with the same instructions.

Measures

Suicide Behaviors Questionnaire (SBQ)—We utilized the 34-item SBQ developed by Linehan and Addis [(15), (Linehan MM, Addis M. Screening for suicidal behaviors: the suicidal behaviors questionnaire, University of Washington, Seattle, WA, USA, 1990, unpublished manuscript)] and recommended for use by the NIMH (16). This self-rated scale measures five domains: past suicidal ideation (SI), future SI, past suicide threats, future suicide attempts (SAs), and the likelihood of dying in a future SA. Suicidal thoughts and related behaviors are rated for the past several days (including today), past month, past four months, past year, and lifetime; recent ideation and related behaviors are weighted higher than past in the total score to assess overall seriousness of SI and behavior in a summary score, ranging from 0–102. The SBQ has high internal reliability (with coefficients ranging from 0.73–0.92), is unidimensional in principal component factor analysis, and has items with good concurrent validity with other scales, such as positive correlation with the Scale for Suicide Ideation, Beck Hopelessness Scale, and Beck Depression Scale ($r = 0.55$ to 0.62), and negative correlation ($r = -0.46$) with Linehan’s Reasons for Living [(15), (Linehan MM, Addis M. Screening for suicidal behaviors: the suicidal behaviors questionnaire, University of Washington, Seattle, WA, USA, 1990, unpublished manuscript)].

Barratt Impulsiveness Scale (BIS-11)—The BIS-11 is a 30-item self-report questionnaire designed to measure levels of impulsiveness (17). Items are rated on a 4-point Likert scale with anchors of ‘rarely/never’ to ‘almost always’. Individual items are summed, with higher total scores representing greater impulsiveness. Previous research has established that the BIS has good psychometric properties in both psychiatric and nonclinical populations (17,18).

Suicide attempts—Suicide attempts between baseline and nine-month prospective follow-up were defined as either (i) a self-reported attempt in the nine-month follow-up packet (“Have you made a suicide attempt in the past 9 months?”), or (ii) the presence of a clinician-reported attempt as a STEP-BD serious adverse event. The level of lethality of past attempts was not specifically assessed in this dataset.

Current smoking at baseline—The self-rated questionnaire packet included a question assessing how many packs of cigarettes per day participants had smoked in the past month. Patients who recorded smoking any amount during the past month were considered to be current smokers.

Statistical analyses

We first examined the univariate association of smoking at baseline with our suicidality variables, the SBQ at baseline and follow-up, as well as prospective suicide attempts at nine-month follow-up. To adjust for potential confounders of the smoking-suicidality relationship, we then performed multivariate regression models for baseline and nine-month suicidality (SBQ scores), including available variables that had been shown or suggested in prior research to be associated with suicidality (12,19). Covariates included gender, lifetime alcohol or substance abuse history, lifetime anxiety disorder, current clinical bipolar status, and age at first episode. These variables were entered into the regression model as a block. We also examined the association of impulsiveness (BIS at baseline) with SBQ scores and whether the smoking-suicidality effect might be explained by impulsivity in an adjusted

regression model. Examination of the distribution of SBQ scores suggests that they are somewhat left-skewed. To confirm the results of the original regression models, all the regression models were run again using a log-transformed SBQ score as the dependent variable in order to assure that the results would remain consistent. Significance was set at $p < 0.05$.

Results

A total of 120 (46%) subjects returned the mailed questionnaires. Of the original 120 subjects, 75 (62.5%) were diagnosed with bipolar I disorder, 30 (25.0%) with bipolar II disorder, and 15 (12.5%) with bipolar disorder not otherwise specified (NOS). Of these, 116 (97%) provided information regarding smoking and had follow-up information regarding suicide attempts, and therefore comprise the study sample. Nine subjects (11%) had missing SBQ data, resulting in a sample size of 107 for baseline SBQ analyses. Of these 107, 79 (74%) had complete SBQ data and covariates at nine-month follow-up. The demographics of the original sample are described in detail elsewhere (12).

Participants were predominantly female, Caucasian, and had at least one comorbid anxiety disorder (see Table 1). Of the 116 participants, 85 (73%) were nonsmokers and 31 (27%) were smokers. Smokers and nonsmokers did not differ by gender, race, clinical status, or prevalence of lifetime anxiety disorders (all p values > 0.05 ; see Table 1). Smokers, however, did have a significantly higher rate of lifetime substance abuse disorders [Fisher's exact test (FET) $p < 0.05$], were significantly younger ($t = 3.49$, $p < 0.0001$), and had a significantly earlier age of bipolar onset ($t = 2.27$, $p < 0.05$; Table 1).

Current smoking was associated with higher SBQ score ($\beta = 11.1$, $SE = 4.3$, $p < 0.05$, adjusted $R^2 = 0.05$) in univariate linear regression analyses. Current smoking status at baseline remained significantly associated with suicidality in the adjusted regression model [$\beta = 9.4$, $SE = 4.6$, $t = 2.1$, $p = 0.042$; full model $F(6,96) = 3.52$, $p = 0.003$, adjusted $R^2 = 0.13$; Table 2] and in the confirmatory model using the log-transformed suicidality score [$\beta = 0.69$, $SE = 0.24$, $t = 2.8$, $p = 0.006$; full model $F(6,96) = 3.28$, $p = 0.006$, adjusted $R^2 = 0.13$]. Suicidality scores were not associated with packs per day of cigarettes smoked ($p = 0.26$), and adding age to the model did not change the relationship between smoking and suicidality.

BIS scores, which have been previously associated with suicidality in bipolar disorder (20–23), were available for 95 of the 107 (89%) subjects in the SBQ sample. We examined the univariate association of impulsivity with SBQ score in this subsample; without adjusting for other variables, BIS was associated with higher SBQ score in a linear regression model [$\beta = 0.4$, $SE = 0.02$, $F(1,93) = 5.0$, $p < 0.05$, adjusted $R^2 = 0.04$]. We then performed an additional exploratory regression of the association of smoking status with SBQ scores, adjusting for BIS score; the association between smoking and current SBQ score was not statistically significant [$\beta = 6.2$, $SE = 4.9$, $t = 1.3$, $p > 0.05$; full model $F(7,82) = 2.9$, $p = 0.009$, adjusted $R^2 = 0.13$], although smokers had numerically higher SBQ scores. In the model using the log-transformed SBQ score, however, smoking remained significantly associated with suicidality, even when accounting for impulsiveness scores [$\beta = 0.599$, $SE = 0.26$, $t = 2.2$, $p = 0.029$; full model $F(7,76) = 2.97$, $p = 0.008$, adjusted $R^2 = 0.14$].

Eight patients (7% of 116) attempted suicide between baseline and nine-month follow-up, with a significantly higher proportion being smokers at baseline (5/31 smokers versus 3/85 nonsmokers, FET $p = 0.031$), consistent with an OR of 5.25 (95% confidence interval: 1.2–23.5). Because this was a secondary analysis of a small sample, the relationship between impulsivity, smoking, and suicide attempts was not examined. Smoking at baseline also

significantly predicted higher SBQ score at nine-month follow-up, after adjustment for gender, lifetime anxiety comorbidity, lifetime substance abuse, age at first bipolar episode, and current bipolar recovery status [$\beta = 12.1$, $SE = 5.4$, $t = 2.2$, $p < 0.05$; full model $F(6,72) = 3.07$, $p = 0.003$, adjusted $R^2 = 0.14$: see Table 3].

Discussion

In this study of 116 individuals with bipolar disorder, current cigarette smoking was associated with suicidal ideation and behavior both at baseline and at nine-month follow-up. Subjects who smoked were significantly more likely to make suicide attempts during the prospective follow-up period, with fivefold increased odds of a prospectively observed suicide attempt in a nine-month follow-up period. These data add to previous findings in bipolar disorder suggesting that the presence of cigarette smoking is a clinical marker for suicide risk.

The finding of increased prospective suicide attempts is particularly striking, building on the work by Oquendo et al. (4), demonstrating that cigarette use predicts suicide attempts prospectively in patients with bipolar disorder. Of interest, previous epidemiologic research has suggested a prospective link between smoking and suicidality even when excluding individuals with depression (24), suggesting that smoking may be a risk factor independent of mood disorders, although some reports did not find this link (25).

That the smoking/suicidality relationship was no longer significant when impulsiveness scores were added to the regression model suggests that the link between smoking and suicide may in part be explained by impulsivity, although power was limited by the relatively small number of smokers, and SBQ scores were higher in this model. (The confirmatory model that used the log-transformed suicidality score, however, did find a statistically significant association between smoking and suicide, even when accounting for impulsivity.) Although suicidality is associated with impulsivity, our finding suggests that smoking status may possibly be associated with suicidality even when impulsivity is controlled for. Nonetheless, the use of smoking status as a marker for increased risk for suicide attempts to identify patients who might need more intensive assessment and/or interventions to maintain their safety is simpler than quantifying impulsivity in a clinical setting. While the predictive value of smoking in and of itself for the identification of patients with bipolar disorder at risk for suicide is small, it may be a useful addition to other clinical risk factors in a comprehensive assessment of suicide risk.

These findings must be interpreted in the context of this study's design and measures. It is possible that smoking status was not correctly classified by our self-report assessment. It is more likely, however, that smoking would have been denied because of the stigma associated with smoking, misclassifying smokers as nonsmokers and biasing the results toward the null hypothesis. Because we did not differentiate between past smokers and nonsmokers, past smokers are included in the nonsmoker group (although their number would be small). This would be expected, however, to bias our findings of an association toward the null, as it is possible that past smokers have higher suicidality than never smokers. Information about nicotine discontinuations was not systematically collected, so the relationship of nicotine withdrawal and cessation with suicidality could not be examined. A causal link between smoking and suicide cannot be drawn from these data. Axis II diagnoses are not known; one retrospective study found that borderline personality disorder may account for the relationship between smoking and suicidality in bipolar disorder, but we did not examine this (26). Further, it remains unknown whether exposure to smoking or nicotine use itself is a risk factor for suicidal behavior and thoughts, or whether being an

individual who smokes is instead a marker for a trait—such as impulsivity—that increases risk for suicidality in individuals with bipolar disorder.

Conclusions

Current cigarette smoking is a predictor of current and nine-month suicidal ideation and behavior in bipolar disorder, and it is likely that impulsivity accounts for some of the relationship between cigarette smoking and suicidality. Current smoking, a simple clinical assessment, should trigger greater attention by clinicians to potential suicidality and become part of a comprehensive assessment of suicide risk. While it is unknown whether reducing nicotine dependence in bipolar disorder would impact suicidality, these results indicate that further research is needed to better understand the link between cigarette smoking and elevated suicidality in bipolar disorder, with attention to personality characteristics, impulsivity, and the effect of periods of fluctuating nicotine use, withdrawal, and discontinuation.

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Table 1Patient characteristics at baseline for smokers and nonsmokers^a

	Nonsmokers at baseline (n = 85)	Smokers at baseline (n = 31)	Overall sample (n = 116)
Gender (female), %	61	58	60
Age, mean (SD) ^b	46.7 (13.5)	37.3 (10.8)	45.0 (13.1)
Race, %			
Non-Caucasian	5	6	5
Caucasian	95	94	95
Clinical status, %			
Recovered/recovering	72	65	70
Any other clinical status	28	35	30
Lifetime substance abuse disorder, % ^c	33	61	41
At least one lifetime anxiety disorder, %	63	83	68
Age of first episode (years), mean (SD) ^c	18.4 (9.4)	14.4 (4.6)	17.2 (8.5)
SBQ total suicidality score, mean (SD) ^b	17.1 (20.0)	28.9 (21.1)	20.4 (20.9)
BIS total, mean (SD)	65.6 (11.8)	70.5 (13.8)	66.9 (12.4)

^a N's vary somewhat due to missing data.^b p < 0.01.^c p < 0.05.

SBQ = Suicide Behaviors Questionnaire; BIS = Barratt Impulsiveness Scale.

Table 2

Adjusted regression model of association between baseline smoking and Suicide Behaviors Questionnaire score^a

Variable	β	SE	<i>t</i>	p-value
Smoking status	9.380	4.550	2.06	0.042
Gender	9.046	4.166	2.17	0.032
Anxiety comorbidity	0.632	4.400	0.14	0.886
Recovery status	-8.566	4.352	-1.97	0.052
Age at first episode	-0.303	0.243	-1.24	0.216
Lifetime substance abuse	-0.179	4.078	-0.04	0.965

^aFull regression model (n = 103); $F(6,96) = 3.52$; adjusted $R^2 = 0.13$; $p = 0.0034$.

Table 3

Adjusted regression model of association between baseline smoking and Suicide Behaviors Questionnaire score at nine-month follow-up^a

Variable	β	SE	<i>t</i>	p-value
Smoking status	12.118	5.410	2.240	0.028
Gender	5.196	5.171	0.318	0.318
Anxiety comorbidity	-1.694	5.447	0.757	0.757
Recovery status	-8.472	4.846	0.085	0.085
Age at first episode	-0.453	0.290	0.122	0.122
Lifetime substance abuse	-2.469	4.723	0.603	0.603

^aFull regression model (n = 79): $F(6,72) = 3.07$; adjusted $R^2 = 0.1372$; $p = 0.0099$.