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Cigarette smoking and its relationship to mood disorder symptoms and co-occurring alcohol and cannabis use disorders following first hospitalization for bipolar disorder

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Abstract

Objectives—Cigarette smoking is highly prevalent among individuals with bipolar disorder (BD) and may adversely affect symptoms of the disorder as well as co-occurrence of other substance use disorders. However, anecdotal reports suggesting that smoking cessation caused a worsening of mood in smokers with BD have raised concerns about quitting. In this study, we prospectively evaluated the course of BD, alcohol use disorders, and cannabis use disorders in relation to smoking and examined the relationship between smoking abstinence and changes in mood.

Methods—Participants (N = 161) were adolescents (n = 80) and adults (n = 81) with bipolar I disorder who were hospitalized for their initial mixed or manic episode. Participants were followed up to eight years post-hospitalization (median follow-up = 122 weeks) as part of a naturalistic, observational study of the longitudinal course of BD and substance use.

Results—Course of BD symptoms in the 12 months following index hospitalization did not differ by smoking status in either the adolescent or the adult subsample. Among adolescents, smoking was associated with increased risk of having a cannabis or alcohol use disorder, almost all of which were new-onset disorders, in the year following first hospitalization. Neither adolescents nor adults who were abstinent from smoking for at least two months experienced significant increases in depressive or manic symptoms.

Conclusions—Although cigarette smoking did not predict a worse course of BD, smoking was associated with increased risk of developing alcohol and cannabis use disorders in adolescents with BD. Importantly, these data provide no evidence to suggest that abstinence from smoking is associated with worsening symptoms of depression or mania in the short term.

Keywords

bipolar disorder; nicotine; tobacco

Tobacco smoking is two to three times more common among people with bipolar disorder (BD) than among individuals without the disorder (1–3) and has dire health consequences.

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In addition to risks of physical illness and early death stemming from tobacco use, cigarette smoking may also worsen the course of BD, affecting mood regulation through its actions on cholinergic, serotonergic, and dopaminergic systems (4, 5) and increasing the rate of metabolism of mood-stabilizing medications (6). Although not all studies agree (7), data from several cross-sectional studies examining correlates of cigarette smoking in this population suggest that smoking is linked to a more severe form of BD marked by greater severity of depression, rapid cycling, psychosis, and increased risk of suicidality (8–10). Several recent reports also suggested that cigarette smoking prospectively predicts worsened BD treatment outcomes (11), including greater overall illness severity, greater severity of depression and mania, and longer periods of hospitalization (12). However, there is a dearth of long-term, prospective studies examining cigarette smoking in relation to the course of BD to advance understanding of this likely complex relationship.

Cigarette smoking is highly correlated with alcohol and other drug use among individuals with BD (7, 9) and in the general population (13). Smoking has also been prospectively linked to an increased risk of both developing (14) and maintaining (15) substance use disorders (SUDs), a particularly prevalent and harmful bipolar comorbidity. However, to our knowledge, there have been no prospective studies examining cigarette smoking as a predictor of the course of SUDs in BD.

Another gap in the literature regarding tobacco smoking among individuals with BD is how initiation of smoking abstinence impacts symptoms of the disorder. There have been a number of single-case reports suggesting that smoking cessation may have precipitated mania (16, 17), and results of a very small ($n = 5$) randomized, controlled trial of bupropion for smoking cessation in individuals with BD indicated that two of the participants (both of whom were in the placebo group) developed hypomania while they were attempting to quit smoking (18). However, the conclusions that can be drawn from this type of evidence are extremely limited, and additional studies involving controlled analyses of larger samples of smokers with BD are needed in order to rule out the possibility that the observed worsening of mood in the weeks following cessation was either coincidental or attributable to nicotine withdrawal, the symptoms of which may mimic depression and/or mania (i.e., insomnia, restlessness, depressed mood, difficulty concentrating, change in appetite or weight, irritability).

The purpose of this study was to examine whether cigarette smoking prospectively predicts a worse course of BD or co-occurring alcohol use disorders (AUDs) and cannabis use disorders (CUDs) following first hospitalization, and whether abstinence from smoking is associated with a worsening of depression or mania/hypomania symptoms. In order to answer these questions, we conducted post-hoc analyses of data collected as part of the University of Cincinnati First Episode Mania Study—a naturalistic, observational study of the longitudinal course of BD and substance use in adolescents and adults with BD. This data set includes up to eight years of follow-up on mood disorder symptoms, symptoms of alcohol and cannabis abuse/dependence, and other indicators of psychiatric status following hospitalization for a mixed or manic episode. Based on the available literature, we hypothesized that with respect to the course of BD, cigarette smoking would prospectively predict poorer recovery in the 12 months following the index hospitalization, including a greater proportion of time with mood disorder syndromes (i.e., depression or mania/hypomania) and a greater incidence of suicide attempts and additional psychiatric hospitalizations. We also hypothesized that smoking would be associated with AUDs and CUDs during that time period. Finally, we conducted an exploratory analysis to determine whether abstinence from smoking at any time point during the study was associated with a worsening of symptoms of depression or mania relative to continued smoking.

Methods

Participants

Study participants were adolescents under the age of 18 ($n = 80$) and adults ($n = 81$) with bipolar I disorder who were hospitalized for the first time (i.e., the index hospitalization) for a manic or mixed episode and who had minimal or no prior treatment with psychotropic medications for BD (i.e., less than 1 month of treatment). Ages ranged from 12 to 45. For adolescents, the mean age was 14 ($SD = 2$), the majority of participants were female ($n = 46$; 58%), and most were White/Caucasian ($n = 62$; 78%). For adults, the mean age was 27 ($SD = 8$), the majority were male ($n = 49$; 61%), and most were White/Caucasian ($n = 50$; 62%).

In order to test our hypotheses regarding the relationship between smoking and symptoms of BD and AUD/CUD in the 12 months following the index hospitalization, we used a subsample ($n = 113$) of this larger group of participants for whom we had smoking data for both the one-month pre-hospitalization period and for at least four months of the post-hospitalization period. This subsample consisted of 72 adolescents and 41 adults. Among the adolescents, the mean age was 14 ($SD = 2$), the majority of participants were female ($n = 43$; 60%), and most were White/Caucasian ($n = 56$; 78%). For the adults, the mean age was 25 ($SD = 7$), the majority of participants were male ($n = 27$; 66%), and most were White/Caucasian ($n = 32$; 78%).

Assessments/procedures

Study assessments were conducted as part of the University of Cincinnati First Episode Mania study, the main findings of which have been published elsewhere, along with a complete description of the methods (19–22). Briefly, adolescents and adults who were hospitalized for a mixed or manic episode between June 1996 and October 2003 at Cincinnati Children's Hospital Medical Center or University Hospital were approached regarding participation in the study. All participants (or the parent/guardian, if the participant was a minor) provided written informed consent to participate, and adolescents under the age of 18 provided their assent to complete the study procedures. The study was reviewed and approved by the Institutional Review Boards of the University of Cincinnati and the Cincinnati Children's Hospital Medical Center.

Index assessments were completed during hospitalization and were used to establish study eligibility and to determine initial severity of symptoms of BD and SUDs. Demographic data were collected from medical chart review and participant self-report. To establish that participants met DSM-IV criteria for bipolar I disorder, either the Structured Clinical Interview for DSM-IV, patient version (SCID-I/P) (23) or the Kiddie Schedule for Affective Disorders–Present and Lifetime version (WASH-U KSADS) (24) was administered by a trained interviewer, and diagnoses were established by study psychiatrists or psychologists. These assessments were also used to establish SUD diagnoses at baseline as well as at study visits subsequent to the index hospitalization. In addition to these diagnostic assessments, the Addiction Severity Index (ASI) (25) was used to determine the severity of AUDs and other SUDs. Severity of BD symptoms was assessed using the Young Mania Rating Scale (YMRS) (26) and the Hamilton Depression Rating Scale (HDRS) (27). The study team has demonstrated strong inter-rater reliability for all of these diagnostic ($\kappa > 0.9$) and symptom measures (intra-class correlation coefficient > 0.7).

Following discharge from the hospital, study visits took place every four months, with the exception of the first visit which occurred one month after discharge. Consistent with our previous work (21, 22) and in order to provide an adequate minimum time to assess post-hospitalization symptoms, our sample included only participants who remained in the study through the four-month study visit. Length of participation for the full sample ($N = 161$)

ranged from 16 to 416 weeks (median = 122 weeks). The percentage of participants reaching major milestones of retention in the study were as follows: 81% remained in the study through the eight-month visit; 79% remained through one year; 58% through two years; 43% through three years; 26% through four years; 21% through five years; and 12% through six or more years.

At each visit, a week-by-week review of symptoms of BD and SUDs over the previous four months was completed using the YMRS, HDRS, and ASI. In order to capture changes in mood and SUD symptoms, raters were instructed to be attentive to the occurrence and timing of symptom worsening or improvement when completing their weekly ratings. Weekly symptom ratings were used to establish the presence and severity of mood and SUD episodes on a 1 to 6 scale. The anchors for this composite symptom rating scale have been reported in detail elsewhere (20), but, briefly, the descriptors for each rating are as follows: 1 = usual self; 2 = residual symptoms; 3 = partial remission; 4 = marked symptoms; 5 = full syndrome; and 6 = full syndrome, severe. Scores at 5 or above are indicative of the presence of BD or SUD syndromes (i.e., depressive or manic/mixed episodes, substance abuse or dependence).

During study visits, participants were also asked about suicidal ideation and attempts, psychiatric hospitalizations, and use of psychotropic medications in the interval since the last visit. Medication adherence was assessed by asking the participant (as well as the participant's family member and/or clinician, if needed) whether, for each prescribed medication, he or she took greater than 75% of the doses, less than 25% of the doses, or somewhere between 25% and 75% of the doses. Taking greater than 75% of the doses was classified as full adherence.

Cigarette smoking was assessed by adding an item to the standard ASI interview. Following the same format used in the ASI to assess the onset and frequency of alcohol and non-nicotine drug use, participants were asked during the index hospitalization about the age-at-onset of regular smoking (i.e., the age at which the participant first smoked three or more times per week for one month or more), the number of years used, and the number of packs of cigarettes smoked per day (PPD) over the prior 30 days. At each of the later study visits, smoking during each month since the last visit was recorded based on the participant's self-report of the number of PPD they had smoked. Smoking status was a dichotomous variable defined as follows: individuals who reported zero PPD during the month prior to the index hospitalization were classified as nonsmokers and those who reported smoking any amount during that month were classified as smokers. For the period following discharge from the index hospitalization, smoking abstinence was defined as two consecutive months of zero PPD. For participants who reported at least two consecutive months of smoking abstinence, the first month at which the participant reported smoking zero PPD was classified as the point of initiation of smoking abstinence.

Statistical analysis

Because of the infrequency of SUDs other than AUDs or CUDs in this sample, we limited our analyses to these two substances. Additionally, due to differences in the smoking behaviors and histories of adult versus adolescent smokers as well as in the nature of childhood- or adolescent-onset versus adult-onset BD, analyses were conducted separately for the adolescent and adult subsamples. To be consistent with prior prospective studies (11, 12), we used baseline smoking status (i.e., smoking during the month prior to hospitalization) in our examination of the relationship between smoking and the course of mood symptoms and co-occurring AUD and CUD (i.e., abuse or dependence on either substance) during the 12 months following the index hospitalization. However, because there were changes in smoking status from pre- to post-hospitalization as well as during the

12-month post-hospitalization period, we also conducted a second set of analyses in which we used the proportion of the 12-month period in which smoking was reported as an alternative indicator of smoking status (i.e., rather than using baseline smoking status). In a previous paper (7), we reported relationships between pre-hospitalization smoking status and presentation of BD and AUD/CUD symptoms at the time of the index hospitalization for a similar subsample of participants; thus, we restricted our analyses for the present study to cigarette smoking in relation to post-hospitalization BD and AUD/CUD symptoms.

To examine smoking in relation to the course of BD and AUD/CUD symptoms, we first identified demographic and baseline clinical variables that significantly differed between smokers and nonsmokers from the following list: age; gender; race; mood state during the index episode (i.e., manic versus mixed); presence of psychosis during the index episode; severity of symptoms at baseline, as indicated by the HDRS and YMRS scores; length of the index episode; and discharge medications (i.e., mood stabilizers, antipsychotics, and antidepressants). Presence of any SUD (including AUD and CUD as well as other SUDs) at the time of hospitalization was also considered as a covariate in predicting the course of BD symptoms. Cox regression was used to examine smoking status as a predictor of time to recovery following hospitalization (i.e., the point at which the participant had eight consecutive weeks of scores ≤ 2 , reflecting usual self or residual symptoms, on the composite symptom rating scale). Percentage of weeks with syndromal depression or mania/hypomania (i.e., scores ≥ 5 on the symptom rating scale) was compared among groups using ANCOVA, and logistic regression analyses were used to determine whether smoking status predicted the occurrence of subsequent psychiatric hospitalizations and suicide attempts during the 12-month period following index hospitalization. Comparison of smoking groups on likelihood of having an AUD or CUD during this time period was conducted using logistic regression.

To examine the relationship between smoking abstinence and changes in symptoms of mania/hypomania and depression, the longest period of smoking abstinence (≥ 2 months) was identified for the abstainer group, and the YMRS and HDRS scores were each averaged over the four weeks prior to initiation of abstinence (to establish a baseline) and over the nine weeks after initiation of abstinence (to assess short-term changes in mood). Although we could have selected a longer period over which to observe the potential relationship between smoking abstinence and mood, by restricting our analyses to the first two months of abstinence we maximized the sample size for this analysis, as almost 64% ($n = 14$ of 22) of those with a two-month period of abstinence later returned to smoking. Changes in scores were calculated for both the YMRS and the HDRS by subtracting the pre-abstinence (i.e., first four weeks) mean from the post-abstinence (i.e., last nine weeks) mean. In order to address the possibility that any observed worsening of mood might represent the natural course of BD rather than the effects of smoking abstinence, change in mood from pre-abstinence to post-abstinence among abstainers was compared with mood changes observed during a random 13-week series of symptom ratings in continuing smokers. A random number generator was used to select a start point for the 13-week series, and the change in the average mood ratings between the first four weeks and the last nine weeks of the series was then calculated. Two ANCOVA analyses were then conducted to compare continuing smokers and abstainers on changes in mood on the YMRS and the HDRS. Similar to the other analyses, we covaried for any variables that differed between continuing smokers and abstainers during the pre-abstinence period, including age; gender; race; taking an antipsychotic or mood stabilizer (with at least 75% adherence); taking bupropion (with at least 75% adherence); taking another antidepressant (with at least 75% adherence); criteria for an AUD or CUD met; and time since hospital discharge. Average scores on the YMRS or HDRS during the pre-abstinence period and time since hospitalization were forced covariates in the analyses of change in symptoms of mania and depression, respectively.

An alpha level of $p < 0.05$ was used for all analyses. Due to the smaller size of the adolescent and adult subsamples and our belief that the risks of inflated type II error outweighed the risks of inflated type I error for this preliminary investigation, no adjustment was made for multiple comparisons. All analyses were conducted using PASW Statistics 18.0.

Results

Cigarette smoking prior to and following index hospitalization

Of the 72 adolescents who provided information about smoking both prior to and following the index hospitalization, 26 (36%) were current smokers (i.e., smoking > 0 PPD within prior 30 days) at the time of index hospitalization. Of the remaining 46 adolescents who were not current smokers at that time, 41 (89%) reported no prior history of regular smoking and 5 (11%) reported a history of regular smoking. On average, adolescents who reported current smoking consumed slightly over one half of a PPD (mean = 0.6 packs, SD = 0.4), had been smoking for two years (SD = 2), and initiated smoking at age 13 (SD = 2). Current smokers differed from current nonsmokers on age and race. As shown in Table 1, adolescent smokers were, on average, approximately one year older than nonsmokers, and there was a higher proportion of White adolescents in the current smoker group ($p < 0.05$).

Smoking status changes between the one-month pre-hospitalization period and the 12-month post-hospitalization period were relatively common among the adolescents; 13 (28%) of the 46 adolescents who were current nonsmokers prior to index hospitalization reported at least one month of smoking in the 12 months following hospital discharge, and 8 (31%) of the 26 adolescents who were current smokers prior to index hospitalization reported at least two consecutive months of nonsmoking during the 12 months following discharge. Over the full length of study participation, 13 of the 42 (31%) adolescents who reported smoking at any point during the study indicated that they had abstained from smoking for two consecutive months, with their longest period of smoking abstinence (≥ 2 months) occurring an average of 19 months (SD = 12) after hospitalization.

Of the 41 adults who provided both pre- and post-index hospitalization smoking data, 23 (56%) reported smoking in the 30 days prior to index hospitalization. Of the 18 adults who were not current smokers at that time, 12 (67%) had no history of regular smoking and 6 (33%) reported regular smoking in the past. On average, current smokers reported that they consumed approximately one PPD (mean = 1.1 packs, SD = 0.6), started smoking at age 16 (SD = 3), and smoked for an average of 9 years (SD = 7). In the adult subsample, there were no significant differences between current smokers and nonsmokers on any of the demographic or clinical characteristics we examined (see Table 1).

In terms of smoking status changes, 5 (28%) of the 18 adults who were not current smokers at the time of the index hospitalization reported smoking during the 12-month post-hospitalization period, and 9 (39%) of the 23 adults who were currently smoking at index hospitalization quit for at least two consecutive months during that same time frame. Over the full length of the study, 9 (32%) of the 28 adults who reported smoking at any point during the study quit for at least two consecutive months, with their longest period of smoking abstinence occurring an average of 18 months (SD = 11) following hospitalization.

Relationship between smoking and the course of BD

Among the adolescents, baseline smoking status did not predict post-hospitalization time to recovery [Wald $\chi^2 = 0.31$, $p = 0.58$; hazard ratio (HR) = 1.37, 95% confidence interval (CI): 0.45–4.15]. Similarly, comparison of the mean percentage of weeks with mood syndromes (i.e., scores ≥ 5 on the composite mood rating scale) indicated that adolescent smokers

(mean = 21.13, SD = 4.09) did not significantly differ from nonsmokers (mean = 13.67, SD = 2.66) on this indicator of psychiatric status [$F(1,68) = 2.71$, $p = 0.10$]. Finally, in the year following the index hospitalization, 20 (28%) of the adolescents were re-hospitalized and 10 (14%) made a suicide attempt. Adolescents who smoked at baseline were no more likely than nonsmokers to report subsequent hospitalization [Wald $\chi^2 = 0.23$, $p = 0.63$; odds ratio (OR) = 1.34, 95% CI: 0.41–4.35] or suicide attempts (Wald $\chi^2 = 0.85$, $p = 0.36$; OR = 2.02, 95% CI: 0.45–9.01). None of these conclusions changed when we used proportion of months of smoking during the 12-month period following index hospitalization instead of baseline smoking status as the indicator of smoking status. Thus, none of the selected measures of the course of BD post-hospitalization showed any significant differences by smoking status among the adolescents.

In the adults, smoking status did not predict time to recovery following hospital discharge (Wald $\chi^2 = 0.08$, $p = 0.77$; HR = 0.89, 95% CI: 0.39–2.03), and smokers (mean = 28.93, SD = 6.96) did not significantly differ from nonsmokers (mean = 22.87, SD = 7.87) on mean percentage of weeks of study participation in which they met full syndromal criteria for depression or mania/hypomania [$F(1,39) = 0.33$, $p = 0.57$]. In the year following discharge from the index hospitalization, nine (22%) of the adults were re-hospitalized and one (2%) made a suicide attempt. Adult smokers were at no higher risk of subsequent hospitalization than nonsmokers (Wald $\chi^2 = 0.01$, $p = 0.97$; OR = 0.97, 95% CI: 0.22–4.31). We were unable to evaluate the relationship between smoking and suicide attempts in the adults because there was only one adult participant who made a suicide attempt in the first year following the index hospitalization. Similar to the findings in adolescents, when we substituted proportion of months of smoking for baseline smoking status in the models, the conclusions did not change.

Relationship between smoking and co-occurring AUD/CUD

Nine (13%) of the adolescents met criteria for a CUD during the first 12 months following index hospitalization, and six (8%) met criteria for an AUD. Eight out of nine (89%) CUDs and all of the AUDs observed during this time period in the adolescents were new-onset disorders (i.e., there was no history of these disorders at the time of the index hospitalization). Cigarette smoking at baseline was associated with increased odds of having AUD/CUD during the 12-month period following the index hospitalization among adolescents (Wald $\chi^2 = 5.82$, $p = 0.02$; OR = 16.62, 95% CI: 1.69–163.13). Proportion of months of smoking during the 12 months following index hospitalization was also associated with AUDs/CUDs during this time period in the adolescents (Wald $\chi^2 = 4.92$, $p = 0.03$; OR = 25.25, 95% CI: 1.46–437.63), mirroring the findings using baseline smoking status as a predictor.

In the 12 months following index hospitalization, seven (17%) of the adult participants met criteria for a CUD and 10 (24%) met criteria for an AUD. Five (71%) of the CUDs and six (60%) of the AUDs were new-onset disorders. Baseline smoking status did not predict the presence of an AUD/CUD in the adults (Wald $\chi^2 = 1.06$, $p = 0.30$; OR = 2.00, 95% CI: 0.53–7.49). The follow-up analysis, in which we substituted proportion of months of smoking during the 12-month post-hospitalization period for baseline smoking status, yielded the same conclusion.

Comparison of mood changes in quitters versus continuing smokers

For the adolescents (see Table 2), after controlling for the initial severity of symptoms, time since hospitalization, and whether the adolescent was taking an antipsychotic or mood stabilizer with at least 75% adherence, change scores on the YMRS from pre- to post-quit were not significantly different for continuing smokers (mean = -1.22, SD = 1.00; 95% CI:

−3.24 to 0.81) and quitters [mean = −1.91, SD = 1.45; 95% CI: −4.84 to 1.03; $F(1,33) = 0.12$, $p = 0.73$]. Similar results were found for the HDRS, where the adolescent continuing smokers (mean = −0.73, SD = 0.65; 95% CI: −2.06 to 0.59) did not differ significantly from the quitters (mean = 0.33, SD = 0.93; 95% CI: −1.56 to 2.22) on change in depressive symptoms, [$F(1,33) = 0.73$, $p = 0.40$].

For the adults (see Table 2) there was a strong relationship between quit status and the presence of an AUD or CUD, with only 1 (4.3%) of the 23 quitters having one or both of these SUDs during the pre-quit period versus 9 (31.0%) of the continuing smokers. Because of its redundancy with the quit status variable, then, we did not include it as a covariate in the analyses. Thus, we controlled only for baseline ratings on the YMRS or HDRS and the time since hospitalization. On the YMRS, continuing adult smokers (mean = −0.96, SD = 0.66; 95% CI: −2.29 to 0.37) did not differ from quitters (mean = 0.58, SD = 0.79; 95% CI: −1.01 to 2.18) on mean change in symptoms of mania [$F(1,46) = 2.01$, $p = 0.16$]. On the HDRS, there was also no difference between continuing smokers (mean = 0.27, SD = 0.54; 95% CI: −0.81 to 1.35) and quitters (mean = 0.55, SD = 0.64; 95% CI: −0.75 to 1.84) on changes in depressive symptoms [$F(1,46) = 0.74$, $p = 0.75$]. Thus, the results of these two analyses indicate that change in mood symptoms following smoking cessation in adult quitters was no different than change in mood symptoms among continuing smokers over a randomly selected period of the same duration.

Discussion

Contrary to our prediction and to the results of a small body of published work on the relationship between cigarette smoking and the course of BD (9, 11, 12), smoking was not related to any of the course of illness variables examined, including time to recovery following hospital discharge, percentage of time with significant mood disorder symptoms, or the likelihood of suicide attempts or subsequent psychiatric hospitalizations. Thus, on the whole, our findings suggest that smoking is not associated with a poorer recovery from a first manic or mixed episode among adolescents and adults with bipolar I disorder. The divergence of our findings from those of the prior studies may be attributable to the fact that data for these analyses were collected as part of a first-episode mania study and are therefore more representative of the relationship between smoking and the early course of the disorder. Additionally, larger samples and/or longer periods of observation may be needed to detect relationships between smoking and lower-frequency events like suicide attempts.

The relationship between cigarette smoking and AUDs and CUDs, which was significant among the adolescents but not the adults, was expected based on prior studies with retrospective designs (9) and on our own previous work demonstrating a relationship between smoking and AUDs/CUDs prior to hospitalization in this sample (7). The observation that smoking predicted development of new-onset AUDs and CUDs among adolescents mirrors the findings of general-population longitudinal cohort studies (14) and suggests that cigarette smoking may be a risk marker for later development of AUDs/CUDs among adolescents with BD. Consequently, young smokers with BD may benefit from targeted prevention strategies to alter that trajectory.

We also found that, on average, smoking abstinence was not associated with an increase in symptoms of depression or mania during the two months following initiation of abstinence. Although some prior investigations of the effect of smoking cessation on psychiatric status have found increased rates of new-onset depression among quitters with a depression history as compared to continuing smokers (28), the majority of studies involving smokers with psychiatric disorders including schizophrenia (29, 30), major depressive disorder (31, 32), and posttraumatic stress disorder (33) have suggested that smoking cessation does not lead

to a deterioration in mental health and may, in fact, improve it (33). In this respect, our preliminary data showing no relationship between smoking abstinence and worsening of mood symptoms in individuals with BD are consistent with previous findings in populations of smokers with other psychiatric disorders. However, since tobacco smoking was not the primary focus of the parent study, there are a number of potential confounds (e.g., use of pharmacotherapies for tobacco cessation other than bupropion) in our analysis of the relationship between smoking abstinence and changes in mood that we either did not assess or could not methodologically control.

In addition to the study limitations already noted above, several other caveats should be mentioned. The primary limitation of the study is the limited assessment of smoking, which did not allow us to distinguish between daily and nondaily smoking, to determine the exact date during the month on which smoking abstinence was initiated, or to determine whether periods of smoking abstinence were deliberate attempts to stop smoking (versus restrictions imposed by parents or institutions, for example). There was also no biochemical verification of smoking status, although, in the case of an observational study, self-report is likely to be a reliable indicator of cigarette use (34). At the same time, retrospective self-report of smoking over a four-month period is likely to be less reliable than assessments conducted at shorter time intervals. We also examined only short-term changes in mood following smoking cessation, and future work should investigate the possibility of delayed onset of depression and mania. Additionally, although our decision to analyze data separately for adolescents and adults is justified by differences that we observed in smoking (e.g., adults tended to be heavier smokers with more consistent patterns of smoking) as well as in the nature of childhood- or adolescent-onset vs. adult-onset BD [e.g., adolescents were less likely than adults to present with a manic (versus mixed) episode, with psychosis, and with a history of co-occurring SUDs], it resulted in a smaller sample size and resultant reduced power. Examining the 95% CI for nonsignificant findings, however, we can be reasonably confident in our findings that smoking abstinence is not associated with a worsening of mood, as the upper limit of the CI for change in symptoms of mania or depression was a maximum of a 1- or 2-point increase, which does not represent a clinically significant worsening of symptoms. On the other hand, the confidence intervals for our analyses of the relationship between smoking and course of BD and AUD/CUD did include effects that would be clinically significant, suggesting that our preliminary findings require additional evaluation with larger samples. Additional study limitations are its limited generalizability to: (i) smokers who have bipolar II disorder or other disorders on the bipolar spectrum for whom the prevalence of smoking is also high; (ii) individuals who use smokeless tobacco; (iii) smokers who have not received treatment for BD; or (iv) most importantly, more chronic populations, since this sample was comprised of only new-onset BD patients.

Despite these limitations, this study has a number of strengths, including its prospective design, the availability of up to eight years of data following initial hospitalization for a manic or mixed episode, and its use of extensive and well-validated symptom assessments. Additionally, the naturalistic, observational nature of the study maximizes the real-world applicability of the findings. Our sample was also unique in that it included younger adolescents (ages 12–14), an age group that has not been included in prior longitudinal studies of the relationship between smoking and symptoms of BD despite the fact that this is a critical time period for observing emergence of both tobacco use and symptoms of mood and SUDs. Finally, the number of participants included in our preliminary analysis of mood changes in quitters compared with continuing smokers is the largest sample to date in which a controlled analysis of the effects of smoking cessation on mood in smokers with BD has been conducted, which is of particular interest given the lack of data available on this topic currently.

Although we did not detect a relationship between cigarette smoking and symptoms of BD following first hospitalization for a manic or mixed episode, there is little question that smoking is detrimental to the physical health and overall well-being of individuals with BD. Smoking cessation is therefore critical for improved health, and our preliminary findings suggest that initiation of smoking abstinence is not associated with a worsening of mood symptoms, although our conclusions are necessarily tentative given the limitations inherent in this secondary analysis. Thus, there is a need for additional studies examining the effects of smoking cessation on mood as well as the safety and efficacy of current treatment approaches for smoking cessation in smokers with BD, particularly given that this group is routinely excluded from studies evaluating new pharmacotherapies and behavioral treatments for tobacco cessation. Greater understanding of the mechanisms underlying the strong relationship between cigarette smoking and BD will also help to inform tobacco cessation treatment for these smokers, including the development of tailored behavioral and pharmacological interventions.

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Table 1

Demographic and clinical characteristics of the subsample (n = 113) by smoking status in the month prior to index hospitalization

	Adolescents			Adults		
	Nonsmoker (n = 46)	Smoker (n = 26)	p-value	Nonsmoker (n = 18)	Smoker (n = 23)	p-value
Demographics						
Age, years, mean (SD)	13.9 (1.5)	14.9 (1.6)	0.01	26.1 (8.3)	24.7 (6.7)	0.58
Sex, female, n (%)	25 (54.3)	18 (69.2)	0.31	6 (33.3)	8 (34.8)	0.99
Race, Caucasian, n (%)	31 (67.4)	25 (96.2)	< 0.01	12 (66.7)	20 (87.0)	0.15
Characteristics of index episode						
Mood state, mixed, n (%)	35 (77.8)	21 (80.8)	0.99	1 (5.6)	8 (34.8)	0.05
Duration episode, weeks mean (SD)	24.2 (29.7)	38.8 (89.2)	0.35	4.8 (6.3)	9.9 (16.8)	0.23
Psychosis, n (%)	15 (33.3)	9 (34.6)	0.99	14 (77.8)	18 (78.3)	0.99
Concurrent SUD, n (%)	0 (0)	1 (3.8)	0.36	2 (11.1)	7 (30.4)	0.25
HDRS score, mean (SD)	16.3 (6.6)	18.9 (6.6)	0.12	12.3 (8.0)	13.1 (8.1)	0.75
YMRS score, mean (SD)	29.2 (8.8)	31.7 (6.6)	0.21	27.9 (9.7)	32.1 (9.1)	0.16
Discharge medications, n (%)						
Antipsychotic	30 (65.2)	16 (61.5)	0.80	12 (66.7)	12 (52.2)	0.52
Mood stabilizer	18 (39.1)	12 (46.2)	0.62	11 (61.1)	15 (65.2)	0.99
Antidepressant	3 (6.5)	2 (7.7)	0.99	2 (11.1)	2 (8.7)	0.99

The p-values in the table were derived from independent samples *t*-tests (for continuous variables) or Fisher's exact tests (for categorical variables). SD = standard deviation; SUD = substance use disorder (includes abuse/dependence diagnoses for all substances except nicotine); HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.

Table 2

Comparison of abstainers and continuing smokers

	Adolescents			Adults	
	Continuing smoker (n = 30)	Abstainer (n = 17)	p-value	Continuing smoker (n = 29)	Abstainer (n = 23)
Demographics					
Age, years, mean (SD)	14.5 (1.6)	15.2 (1.5)	0.12	26.9 (7.6)	26.5 (7.1)
Sex, female, n (%)	19 (63.3)	12 (70.6)	0.75	10 (34.5)	8 (34.8)
Race, Caucasian, n (%)	28 (93.3)	14 (82.4)	0.34	23 (79.3)	12 (52.2)
Severity of BD and AUD/CUD symptoms^a					
AUD or CUD, n (%)	4 (13.3)	1 (5.9)	0.64	9 (31.0)	1 (4.3)
HDRS score, mean (SD)	6.1 (4.2)	6.8 (4.9)	0.61	4.4 (4.0)	5.0 (5.2)
YMRS score, mean (SD)	12.9 (7.6)	8.8 (7.5)	0.09	9.6 (8.9)	8.8 (8.5)
Medications, n (%)^d					
Antipsychotic or mood stabilizer	19 (76.0)	7 (41.2)	0.03	15 (60.0)	10 (43.5)
Bupropion	2 (6.7)	3 (17.6)	0.34	1 (3.4)	1 (4.3)
Other antidepressant	2 (8.0)	4 (23.5)	0.20	2 (7.7)	3 (13.0)
Time since index hospitalization, weeks, mean (SD)^b	35.9 (29.8)	90.4 (52.0)	< 0.01	50.1 (70.5)	138.3 (94.6)
					< 0.01

The p-values in the table were derived from independent samples *t*-tests (for continuous variables) or Fisher's exact tests (for categorical variables). SD = standard deviation; BD = bipolar disorder; AUD = alcohol use disorder; CUD = cannabis use disorder; HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.

^aDuring the pre-abstinence period.

^bRepresents time until start of the 13-week period over which changes in mood were assessed.