Nicotine intake and smoking topography in smokers with bipolar disorder

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Abstract

\textbf{Objectives}—Cigarette smoking behavior in bipolar disorder (BPD), including the effects of mood-stabilizing medications, has not been well characterized.

\textbf{Methods}—We compared serum nicotine, nicotine metabolite levels, and smoking topography in 75 smokers with BPD to 86 control smokers (CON). For some comparisons, an additional control group of 75 smokers with schizophrenia (SCZ) were included.

\textbf{Results}—There were no differences between the BPD and CON groups in baseline smoking characteristics or serum nicotine or cotinine levels. Fifty-one smokers with BPD (68.9\%) were taking one of the following mood stabilizers: valproic acid, lamotrigine, carbamazepine, oxcarbazepine, lithium, or topiramate. The 3-hydroxycotinine-to-cotinine ratio, a marker of cytochrome P450 2A6 (CYP2A6) metabolic activity, was significantly higher in BPD versus CON and versus SCZ (0.68 versus 0.49 versus 0.54; \( p = 0.002 \)). The difference between groups, however, was no longer significant when the analysis was repeated with those taking hepatic enzyme-inducing drugs (carbamazepine, oxcarbazepine, and topiramate) included as a covariate. The time between puffs, or interpuff interval (IPI), was shorter in BPD versus CON by an average of 3.0 sec (\( p < 0.05 \)), although this was no longer significant when we removed smokers from the analysis of those taking hepatic enzyme inducers.

\textbf{Conclusions}—Smokers with BPD are not different from CON on most measures of nicotine intake and smoking topography. We found an increased rate of nicotine metabolism in smokers taking mood stabilizers that are hepatic enzyme inducers, including carbamazepine, oxcarbazepine, and topiramate. Smokers with rapid nicotine metabolism might be expected to smoke more intensely to compensate for the more rapid disappearance of nicotine from the blood and brain, and may have more difficulty in quitting smoking, although this requires further study.
Smokers with serious mental illness are disproportionately heavy users of tobacco, and smoking remains a leading cause of death and disease for this group (1–3). In particular, smoking is more prevalent and quit rates are lower in the more severe forms of mental illness, such as schizophrenia (SCZ) and bipolar disorder (BPD), than in the general population, (1, 4–7). Some studies have found similar smoking prevalence rates and patterns among those with SCZ and BPD (8, 9), suggesting overlap and similarity among smokers in these groups.

Cigarette smoking is common in BPD, with prevalence rates of about 60% in various studies (1, 4), and heavy smoking has also been found to be common in patients with this condition (10). Smoking in BPD is linked to more severe illness and worse clinical outcomes on a variety of measures, including earlier onset of illness, more suicidality, poorer functioning, greater symptom severity, more substance use and presence of psychotic symptoms (7, 11–14). Clinical trial data indicate that smokers with BPD experience a reduced treatment response and more discontinuation of treatment compared to nonsmokers (15).

Heavy and intense smoking behavior has been well documented in SCZ. Findings include (all compared to controls without mental illness) higher serum levels of nicotine and nicotine metabolites, greater nicotine intake from a single cigarette, and more intense cigarette puffing, characterized by rapid puffing and a short time between puffs [also called the interpuff interval (IPI) (16–19)]. Theories about high nicotine intake in SCZ link the behavior to abnormalities in brain nicotinic receptor function, although we have little explanation for why other seriously mentally ill subgroups also smoke more frequently and heavily than smokers without mental illness. It is possible that smoking behaviors observed in SCZ may be related to psychotic symptomatology in general, and not specific to SCZ. About half of manic episodes have psychotic features, and patients with BPD and a history of experiencing at least one psychotic symptom are more likely to be current and heavy smokers [defined as more than 20 cigarettes per day (CPD)], compared to those without psychosis (7, 20).

Use of medication may also influence smoking behavior. Although studies of smoking in SCZ have generally found that antipsychotic medication does not seem to influence nicotine intake and smoking behavior (16, 18), these studies are, at least to some degree, confounded by the fact that all subjects are taking it. Studying the effect of antipsychotic medications on smoking in BPD is relevant, as many atypical antipsychotic agents have now been approved by the Food and Drug Administration for the treatment of mania. Anti-epileptic drugs (AEDs) are increasingly used in the management of serious mental illness, and our prior work found that carbamazepine (CBZ) and oxcarbazepine (OCB), but not valproic acid (VPA), resulted in increased nicotine metabolism, as measured by the ratio of the nicotine metabolites 3-hydroxycotinine (3-HC) to cotinine (COT), also called the nicotine metabolite ratio (NMR) (21). The NMR is a biomarker of the activity of the drug-metabolizing enzyme cyto-chrome P450 2A6 (CYP2A6) (22, 23). Lastly, some have argued that because of various clinical, epidemiologic, and genetic similarities, BPD and SCZ represent a disease continuum (24, 25) which creates the potential for similar smoking behaviors in these groups that have previously not been studied.

The objective of the present study was to measure serum nicotine and metabolite levels and characterize cigarette smoking behavior in smokers with BPD and compare these to control
smokers without mental illness. We used the NMR to compare nicotine metabolism between these groups. The study was part of a larger study that also included smokers with SCZ who underwent the same procedures (18).

**Methods**

**Subjects**

This study was approved by the Institutional Review Board at UMDNJ–Robert Wood Johnson Medical School (New Brunswick, NJ, USA). Subjects were recruited from the UMDNJ–University Behavioral Health Care System and other outpatient behavioral health care agencies. A community sample of healthy volunteer smokers without mental illness was recruited through advertisements to participate in the study. All subjects with BPD were enrolled in mental health treatment and had their diagnosis confirmed using the Structured Clinical Interview for DSM–IV (SCID) (26). Control smokers (CON) had to be without any mental illness within the previous year (SCID confirmed) and could not have taken an antidepressant, mood stabilizer, or anxiolytic drug for any reason within the previous six months. All subjects were ≥18 years of age, smoked ten or more CPD, and had a baseline expired carbon monoxide (CO) level greater than 8 parts per million (ppm). CO levels were assessed by having participants take a deep breath and hold it for 15 sec before exhaling into a handheld CO monitor (EC-50 Smokerlyzer; Bedfont Scientific, Williamsburg, VA, USA). Subjects using tobacco products other than cigarettes, pregnant smokers, or anyone with an active substance use problem [as defined by a Drug Abuse Screening Test score ≥6 (27) or Alcohol Use Disorders Identification Test score ≥8 in men and ≥7 in women (28)] were excluded. Those using any tobacco treatment medications were also excluded. Participants were paid US$15 for baseline assessments and US$85 for the completion of all measurements on Day 3.

From these recruitment efforts, 631 potential participants were screened for eligibility, although most were screen failures for not meeting diagnostic criteria. A total of 188 who met the eligibility criteria gave signed informed consent to participate, consisting of 88 smokers with BPD and 100 CON. Data from 25 participants were later excluded for subjects not meeting the eligibility criteria (n = 6), being lost to follow-up/not completing the study (n = 10), violating the research protocol (n = 6), and one participant wanted their data and blood specimens discarded. An additional three subjects were not included in the analyses because they did not have a complete dataset (lacking topography or serum nicotine measures). Therefore, for the purposes of the study, analyses were conducted on 161 participants (BPD (n = 75) and CON (n = 86)) who completed all study procedures. Since the data came from a larger study that also included smokers with SCZ, we included the smokers with SCZ (n = 75) as an additional comparison group for some analyses. For further review of these subjects please refer to Williams et al. (18).

**Procedures**

After signing the consent form, subjects completed an assessment battery including a smoking history, an expired CO measurement, demographic and medication questionnaires, and the Fagerstrom Test for Nicotine Dependence (FTND) (29). Weight, body mass index, and vital signs were recorded and a urine pregnancy test given to female subjects of childbearing age, to rule out pregnancy. Psychological symptoms were assessed in subjects with mental illness using the Positive and Negative Syndrome Scale (PANSS) (30), the Montgomery–Åsberg Depression Rating Scale (MADRS) (31), and the Young Mania Rating Scale (YMRS) (32). Subjects were required to bring their own cigarettes for all study procedures, which took place on three consecutive days.
Following completion of the questionnaires, participants were trained on the proper use of the topography device and were observed smoking with the device during practice topography sessions on Days 1 and 2. The Clinical Research Support System (CReSS) Micro Smoking Topography device (Plowshare/Borgwaldt-KC, Richmond, VA, USA) is a battery-operated device that measures a full complement of smoking behaviors, including puff volume, quantity of puffs, puff duration, average flow, IPI, time, and date. Although this device uses a mouthpiece, cigarette smoking has been shown not to change as a function of smoking through a mouthpiece (33, 34). The CReSS Micro Smoking Topography device detects cigarette insertion and removal and automatically captures all puff measurements. Following the study procedures, the data are transferred from the handheld device to a desktop computer program.

Subjects were then scheduled for a final study day (Day 3), during which time they would have an all-day assessment of smoking topography with measurement of nicotine blood levels. On the afternoon prior to Day 3, subjects had a brief appointment to review instructions. They took the topography device home with them and began using it for all cigarettes smoked ad libitum, starting at around 3:00 p.m. They were also instructed to use the device for all cigarettes smoked upon awakening the next day, including the first cigarette of the day, prior to returning to the laboratory for a 9:00 a.m. appointment.

Subjects arrived at the laboratory at 9:00 a.m. on Day 3 and were not allowed to smoke from 9:00 to 10:00 a.m., to standardize time for the first blood collection. Subjects completed brief questionnaires assessing their urges to smoke [Questionnaire of Smoking Urges Brief Form (QSU) (35)] and mood states [Positive and Negative Affect Schedule (PANAS) (36)]. At 10:00 a.m., subjects had a baseline (pre-cigarette) expired CO reading and a pre-cigarette venous blood draw. Following this, subjects were instructed to smoke one of their own cigarettes. Immediately after smoking, subjects had a repeat (post-cigarette) CO reading and blood draw. They were then instructed to use the topography device for all cigarettes they smoked that day (unsupervised) and to return to the laboratory at 3 p.m. for the final blood draw and CO reading. Measurement of nicotine levels at three time points was done to assess both the nicotine intake that occurs from smoking a single morning cigarette, and also the nicotine intake throughout the day, and to compare these with topography measures at different time points throughout the day. Studies of nicotine regulation show that during ad libitum smoking, blood nicotine concentrations gradually rise through the morning hours, plateau around noon, and remain relatively stable until bedtime, making 3:00 p.m. an ideal collection time (37). At each time point, a 10 mL sample of blood was collected in a serum tube, centrifuged for 15 min and frozen at −20°C for later analysis. Specimens were sent to the Clinical Pharmacology Laboratory at San Francisco General Hospital, University of California, for analysis of nicotine, COT, and trans 3-HC, which were quantified using liquid chromatography–mass spectrometry (38). Data retrieval and sanitization from the CReSS Micro Smoking Topography device were performed in accordance with the manufacturer’s instructions.

**Statistical analysis**

Analysis of variance and chi-square tests were used to compare all three groups on baseline characteristics, including sociodemographic and smoking variables. Two sample t-tests were used to compare symptom scores between the BPD and SCZ groups. Baseline CO (in ppm), average number of CPD, and serum nicotine values were compared between BPD and CON groups using a two-sample t-test. Ratios of 3-HC:COT were calculated for all subjects. Serum COT values and the 3-HC:COT ratio were compared between groups using the nonparametric Wilcoxon or Kruskal–Wallis tests because of the right-skewed distributions. Analysis of covariance (ANCOVA) of log-transformed 3-HC:COT ratios was used to examine differences between the diagnostic groups, including medications as covariates.
Antipsychotic medication dose was converted to chlorpromazine (CPZ) equivalents (39) to standardize and compare dose across different medications.

We used a data-cleaning procedure (Plowshare Technologies, Richmond, VA, USA) for smoking topography data, to identify and delete erroneous puffs/cigarettes, which are beyond the normal physiologic measures and can result from movement artifact. The criteria for false puffs include puff volume greater than 150 mL, average flow rate less than 15 mL/sec, peak flow rate less than 16 mL/sec, and duration greater than 2800 msec. We also considered puffs with an IPI of greater than 90 sec to be aberrant and these were deleted from the analysis (this represented 0.3% of the dataset). Less than 5% of puffs were defined as aberrant based on any of the above criteria. In addition to the values derived by the topography machine, we calculated several additional variables. Total cigarette puff volume (mL) was derived by adding puff volumes for each cigarette and total cigarette puff rate (puffs/min) was derived by dividing the total number of puffs per cigarette by the total time taken to finish that cigarette.

Mean values of repeatedly measured topography variables were estimated and compared using random effects linear regression (40). The diagnosis group was treated as the fixed effect, and subjects and cigarettes were treated as random effects to account for the within-subject correlation and the double-nested structure of data (puffs within cigarettes and cigarettes within subjects). To assess the association between topography variables and rate of nicotine metabolism (3-HC:COT ratio), we used a weighted linear regression analysis with the change in the 3-HC:COT ratio as the dependent variable and each mean smoking topography measure as the covariate. This analysis was weighted by the inverse of the standard error of the mean (SEM) to account for the variation between repeatedly measured topography data, and mean measures with better precision (smaller standard error) were given more weight in the regression analysis.

A p-value <0.05 was considered to be statistically significant. Bonferroni corrections were applied to adjust for type I error rates resulting from multiple comparisons, as appropriate. All statistical analyses were performed using SPSS v17 (IBM Corporation, Armonk, NY, USA) and SAS v9.1 (SAS Institute, Cary, NC, USA).

Results

Demographics

No differences were found between BPD and CON on demographic characteristics, including age, education, CPD, and measures of nicotine dependence, including FTND total score and time to first cigarette smoked in the morning (TTFC) (see Table 1). Demographic information for the SCZ sample is included in Table 1 as an additional reference group. The BPD group included more Caucasians and fewer African Americans compared to the CON group. Subjects with BPD were relatively euthymic, with low scores on scales for depression (MADRS), mania (YMRS), and psychosis (PANSS). About half the sample (49.3%) had a past or present history of psychotic symptoms. Only one BPD patient was not taking any psychiatric medications and the majority of patients (71.6%) were taking an antipsychotic medication. Of those taking an antipsychotic drug, the vast majority (95%) were atypical antipsychotic agents and the average antipsychotic dose was 283.7 (standard deviation = 388.9) CPZ equivalents. Fifty-one smokers (68.9%) with BPD were taking one of the following mood stabilizers: valproic acid, lamotrigine, carbamazepine, oxcarbazepine, lithium, or topiramate, where valproic acid refers to all its formulations. Nine smokers (31.1%) with BPD were taking more than one mood stabilizer. Groups differed significantly in PANAS scores. Smokers with BPD had higher PANAS negative scores (12.2 versus 5.2, p < 0.001) and lower PANAS positive scores (22.6 versus 27.0, p < 0.01) as compared to

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CON. Craving scores were no different between BPD and CON groups, as measured by the QSU, although the Factor 2 scores were significantly higher in SCZ.

**Comparison of serum nicotine and nicotine metabolite levels**

Serum nicotine levels were measured three times on study Day 3: before (PRE) and after (POST) smoking a single timed morning cigarette at approximately 10:00 a.m. and again at 3:00 p.m. There were no significant differences in nicotine levels between BPD and CON smokers measured at each respective time point (Table 2). The increase in serum nicotine concentration from before to after the 10:00 a.m. cigarette (nicotine boost) was also not significantly different between groups (12.4 versus 14.3 ng/mL; t = −1.474, p = 0.142). Similarly, serum COT levels and expired CO levels were no different between BPD and CON smokers at all time points (3:00 p.m. COT values shown in Table 2). We repeated these analyses in the BPD sample (excluding the control smokers) and found no differences in nicotine or COT levels between BPD smokers with (versus without) a history of psychosis or BPD smokers taking (versus not taking) an antipsychotic medication. By contrast, smokers with SCZ had significantly higher nicotine and serum COT levels than CON and BPD smokers (see Fig. 1).

**Hydroxycotinine:COT ratio**

The 3-HC:COT ratio was significantly higher in BPD smokers than in both CON and SCZ groups (0.68 versus 0.49 and 0.54, respectively; F(2,231)=5.28, p = 0.002 (Fig. 1)). Serum levels of 3-HC were also significantly higher in BPD smokers than in CON (147.2 versus 105.7; t = 3.56, p = 0.003). Because of the potential confounding effects of race on nicotine metabolism (41), we conducted a sensitivity analysis looking at the 3-HC:COT ratios in the subset of Caucasians versus African Americans in the sample (which included 84% of our subjects). Sensitivity analyses were done within and across diagnosis groups. In the entire sample, African Americans had a significantly lower 3-HC:COT ratio compared to Caucasians (0.38 versus 0.69, p < 0.001), indicating slower nicotine metabolism in African Americans. This difference remained even in the diagnostic subgroups, although the ratios in both BPD racial groups were higher than in the CON of the same race (BPD African American 0.51 versus BPD Caucasian 0.76).

We also repeated the analysis on the log-transformed 3-HC:COT ratios to examine the effects of smokers taking hepatic enzyme-inducing medications. We classified the hepatic enzyme inducers as carbamazepine, oxcarbazepine, and topiramate based on our previous work (21) and the literature suggesting that topiramate is a weak hepatic enzyme inducer (42). When the hepatic enzyme-inducing drugs (carbamazepine, oxcarbazepine, and topiramate) were included as a covariate, the difference in 3-HC:COT ratios between the diagnostic groups was no longer significant (p = 0.257). We also combined groups with SCZ and BPD to evaluate the effects of specific medications on the 3-HC:COT ratio. The mean nicotine metabolite ratio was highest in smokers with BPS or SCZ taking carbamazepine or oxcarbazepine, although still higher in those taking topiramate versus not taking any of these medications (1.11 versus 0.72 versus 0.53, respectively). A total of seven smokers with BPD or SCZ were taking topiramate (one was excluded from analysis because they were also taking carbamazepine). The trend in higher 3-HC:COT ratios in smokers taking topiramate was not significant in this small sample (0.72 versus 0.53; 95% confidence interval (CI): 2.00–0.25, p = 0.07).

**Comparison between smoking topography measures during 24-hour smoking session**

During the 24 ± 2 hour assessment period, a total of 2762 cigarettes were smoked by BPD and CON subjects. This included data on 32077 individual puffs. Smokers with BPD differed significantly from CON in several measures of smoking topography (see Table 3).
There were no differences in the average number of cigarettes smoked in a 24-hour testing session among smokers with BPD as compared to control smokers (mean 18.0 versus 16.3; \( t = 1.74; p = 0.08 \)). The IPI was shorter in BPD by an average of 3.0 sec (\( p < 0.05 \)). Smokers with BPD had a greater total puff volume than CON (\( p < 0.05 \)) and a faster average cigarette puff rate (\( p < 0.01 \)). We repeated these analyses in the BPD sample and found no differences in topography variables between BPD smokers with (versus without) a history of psychosis or BPD smokers taking (versus not taking) an antipsychotic medication. We also repeated the analyses removing the individuals with BPD taking one of the hepatic enzyme-inducing medications (\( n = 16 \)). When these subjects were removed from the sample, there were no longer significant differences in IPI between groups.

We conducted analyses to examine in the association between the 3-HC:COT ratio and smoking topography variables. For all subjects (BPD and CON), a decrease in IPI by 1 sec was associated with an increase in the 3-HC:COT ratio of 0.0086 ng/mL (mean = −0.0086, SEM = 0.0042; 95% CI: −0.0171 to −0.0003, \( p < 0.05 \)). No associations with other smoking topography variables in BPD versus CON were found to be statistically significant (data not shown).

**Discussion**

Serum nicotine and COT concentrations in smokers with BPD did not differ from those in control smokers without mental illness. This was in contrast to smokers with SCZ, who had higher levels of nicotine from the same number of cigarettes smoked per day. Interestingly, a history of psychosis did not predict greater nicotine intake in smokers with BPD in the present study. Taking an antipsychotic medication similarly did not predict greater nicotine intake, and a high number of BPD subjects reported taking antipsychotic medication.

Seventy to eighty percent of systemically absorbed nicotine is metabolized in the liver by the enzyme CYP2A6 to COT, which is further metabolized into 3-HC by CYP2A6 (43). The 3-HC:COT ratio is a noninvasive marker of CYP2A6 metabolic activity and is highly correlated with the rate of nicotine metabolism (38). The NMR (3-HC:COT) in the present study was significantly higher in BPD patients, although this effect was not present when we controlled for those taking hepatic enzyme-inducing antimanic medications. While it is possible that excluding these subjects reduced the statistical power of our tests, we believe that it is more likely that hepatic enzyme-inducing mood-stabilizer medications were responsible for the higher nicotine metabolite ratio in smokers with BPD. Given the trend for higher NMR ratios in individuals taking topirimate, we suspect that this agent increases nicotine metabolism, although we cannot confirm it in this small sample.

People with variants in the *CYP2A6* gene that controls the rate of nicotine metabolism differ in their smoking behavior and their propensity toward nicotine dependence. On average, slow metabolizers smoke fewer cigarettes per day, for fewer years, and are more likely to quit in their lifetime compared to fast metabolizers (44–48). Fast metabolizers experience more craving in a smoking cessation attempt and are less likely to stop smoking compared to slow metabolizers using the same treatments (49, 50). Fast metabolizers may experience a lowered therapeutic response to traditional doses of nicotine replacement medications. It is not known if these same effects are seen when rapid metabolism is due to metabolic interactions and not genetic predisposition, although this warrants further study.

Our data corroborated other findings (41, 51, 52) that African American smokers metabolize nicotine slower than Caucasian smokers. Our data may have been impacted by the low prevalence of African Americans with BPD in the present study. Race is an important characteristic to consider in future studies, as others have found that African Americans are
over-diagnosed with SCZ and under-diagnosed with BPD (53). CYP2A6 activity is also important in the activation of toxic and procarcinogenic compounds found in tobacco smoke (54–56). We found significantly higher total puff volume in smokers with BPD. Total puff volume per cigarette is a function of puff number and volume per puff, and is a good index of the ‘work’ that the smoker performs in smoking the cigarette (57). Estimates of total smoke exposure are essential to understanding differential toxic chemical exposures that result from smoking (58).

Smokers with rapid metabolism of nicotine would be expected to smoke more intensely to compensate for the more rapid disappearance of nicotine from the blood, and presumably brain. This behavior is consistent with our finding of a shorter IPI in BPD smokers. Prior work in this area, including our own, has shown that shorter IPI is associated with increases in nicotine intake (18, 59), suggesting that this effect is not unique to mental illness but is a mechanism associated with an intensity of cigarette smoking. Other studies of topography have found an association between the 3-HC:COT ratio and greater total puff volume, suggesting more intense puffing in fast metabolizers, although via a different puffing mechanism (60, 61). This may also contribute to greater difficulty in quitting smoking. The findings of this study support an increased rate of nicotine metabolism in smokers with BPD taking carbamazepine, oxcarbazepine, and topiramate. As these medications are commonly used for a range of psychiatric and nonpsychiatric conditions, further studies should explore their potential effects on smoking behavior and ability to quit smoking.

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Fig. 1.
Nicotine and metabolite levels in smokers with schizophrenia (SCZ), bipolar disorder (BPD), and controls [(CON) without mental illness]. (A) Mean serum nicotine levels (ng/mL). (B) Mean serum cotinine levels (ng/mL). (C) Mean serum 3-hydroxy-cotinine (HC) levels (ng/mL). (D) Mean 3-HC:cotinine ratios. ns = not statistically significant.
Table 1
Baseline characteristics of smokers with BPD, smokers with SCZ, and CON smokers (N = 236)

|                          | BPD (n = 75) | SCZ (n = 75) | CON (n = 86) | p-value$^d$ |
|--------------------------|--------------|--------------|--------------|-------------|
|                          | Mean (SD)    | Mean (SD)    | Mean (SD)    |             |
| Cigarettes per day       | 19.7 (8.0)   | 22.3 (11.5)  | 20.0 (7.7)   | 0.160       |
| Baseline CO level (ppm)  | 19.7 (11.0)  | 23.1 (12.2)  | 19.5 (7.6)   | 0.057       |
| FTND                     | 5.9 (2.0)    | 5.9 (2.0)    | 5.5 (1.9)    | 0.248       |
| No. years smoked         | 21.6 (12.2)  | 28.1 (11.9)  | 20.4 (11.5)  | < 0.001     |
| Age first smoked, years  | 14.2 (4.3)   | 14.7 (5.2)   | 14.7 (3.7)   | 0.676       |
| Age, years               | 38.9 (11.6)  | 45.7 (10.5)  | 38.0 (12.0)  | < 0.001     |

|                          | Count (%)    | Count (%)    | Count (%)    | p-value$^d$ |
|--------------------------|--------------|--------------|--------------|-------------|
| Gender                   |              |              |              | 0.012       |
| Male                     | 42 (56.0)    | 55 (73.3)    | 44 (51.2)    |             |
| Female                   | 33 (44.0)    | 20 (26.7)    | 42 (48.8)    |             |
| Race/ethnicity           |              |              |              | 0.002       |
| African American         | 12 (16.0)    | 35 (46.7)    | 25 (29.1)    |             |
| Caucasian                | 53 (70.7)    | 33 (44.0)    | 45 (52.3)    |             |
| Hispanic                 | 6 (8.0)      | 4 (5.3)      | 13 (15.1)    |             |
| Other                    | 4 (5.3)      | 3 (4.0)      | 3 (3.5)      |             |
| Education                |              |              |              | 0.166       |
| No high school           | 16 (21.3)    | 23 (30.7)    | 15 (17.4)    |             |
| High school/GED          | 27 (36.0)    | 31 (41.3)    | 41 (47.7)    |             |
| Some college             | 23 (30.7)    | 17 (22.7)    | 26 (30.2)    |             |
| Bachelor’s degree or higher | 9 (12.0) | 4 (5.3) | 4 (4.7) |             |
| TTFC (≤ 30 min)          | 69 (92.0)    | 71 (95.0)    | 73 (85.0)    | 0.119       |
| MADRS score              | 10.6 (8.0)   | 10.2 (8.0)   | –            | 0.248       |
| YMRS score               | 3.9 (5.7)    | 2.6 (4.5)    | –            | 0.225       |
| PANSS positive score     | 12.9 (4.8)   | 18.4 (6.1)   | –            | < 0.001     |
| QSU Factor 1 scale       | 46.4 (32.5)  | 53.9 (32.9)  | 50.5 (33.5)  | 0.376       |
| QSU Factor 2 scale       | 26.8 (28.3)  | 39.0 (31.1)  | 20.6 (24.2)  | < 0.001     |
| QSU general factor       | 38.6 (28.6)  | 49.7 (30.6)  | 39.3 (27.1)  | 0.114       |
| PANAS negative           | 12.2 (9.9)   | 7.7 (7.5)    | 5.2 (7.0)    | < 0.001     |
| PANAS positive           | 22.6 (9.2)   | 22.5 (9.5)   | 27.0 (7.5)   | 0.001       |
| Medications              |              |              |              |             |
| Valproic acid            | 21 (28.4)    | 14 (19.2)    | –            | –           |
| Lamotrigine              | 14 (18.9)    | 3 (4.1)      | –            | –           |
| Carbamazepine or Oxcarbazepine | 10 (13.5) | 4 (5.5) | – | – |
| Lithium                  | 9 (12.2)     | 4 (5.5)      | –            | –           |
| Topiramate               | 7 (9.5)      | 1 (1.4)      | –            | –           |
|                                | BPD (n = 75) | SCZ (n = 75) | CON (n = 86) | p-value$^a$ |
|--------------------------------|--------------|--------------|--------------|-------------|
| More than one mood stabilizer  | 9 (12.2)     | 4 (5.5)      | –            | –           |
| No mood stabilizer             | 23 (31.1)    | 53 (72.6)    | –            | –           |
| Antidepressant                 | 33 (44.6)    | 27 (37.0)    | –            | –           |
| Benzodiazepine                 | 14 (18.9)    | 6 (8.2)      | –            | –           |
| Antipsychotic                  | 56 (75.7)    | 73 (100)     | –            | –           |

BPD, bipolar disorder; CO = carbon monoxide; CON, control; FTND = Fagerstrom Test for Nicotine Dependence; GED = General Educational Development; MADRS = Montgomery–Åsberg Depression Rating Scale; PANAS = Positive and Negative Affect Schedule; PANSS = Positive and Negative Syndrome Scale; QSU = Questionnaire of Smoking Urges Brief Form; SCZ, schizophrenia; TTFC = time to first cigarette smoked in the morning; YMRS = Young Mania Rating Scale.

$^a$Analysis of variance (ANOVA), independent sample t-test, or chi-square test.
## Table 2

Smoking biomarkers in smokers with bipolar disorder and control smokers without mental illness

|                    | CPD  | Serum PRE nicotine (ng/mL) | CO PRE nicotine (ppm) | Serum POST nicotine (ng/mL) | CO POST nicotine (ppm) | Serum 3 PM nicotine (ng/mL) | CO 3 PM (ppm) | COT/CPD ratio | 3-HC/COT ratio |
|--------------------|------|-----------------------------|------------------------|-----------------------------|------------------------|-----------------------------|----------------|---------------|----------------|
| Bipolar disorder (n = 75) | 19.7 (8.0) | 17.8 (9.6) | 18.8 (8.8) | 30.2 (11.2) | 22.6 (8.5) | 25.6 (12.8) | 321.1 (151.4) | 24.3 (10.6) | 18.5 (11.4) | 0.7 (0.5) |
| Controls (n = 86) | 20.0 (7.4) | 16.3 (8.2) | 17.7 (8.0) | 30.6 (10.5) | 21.6 (7.8) | 24.4 (10.6) | 303.9 (128.1) | 23.0 (9.3) | 16.7 (8.5) | 0.5 (0.3) |

Values are presented as mean (standard deviation). CO = carbon monoxide; COT = cotinine; CPD = cigarettes per day; HC = hydroxycotinine; 3 PM = 3:00 p.m.

\[ ^a \text{p} < 0.01. \]
Table 3
Summary of topography results using CReSSMicro (N = 161)

|                                | Bipolar disorder (n = 75) | Controls (n = 86) | Bipolar disorder/controls |
|--------------------------------|---------------------------|-------------------|--------------------------|
|                                | Mean (SE)\(^a\)          | Mean (SE)\(^a\)   | Mean (SE)\(^a\)          | p-value     |
| Puffs per cigarette (puff count) | 13.1 (0.15)               | 12.3 (0.15)       | 0.9 (0.67)               | 0.182       |
| Interpuff interval (sec)       | 18.4 (0.13)               | 21.0 (0.14)       | -3.0 (1.21)              | 0.015       |
| Mean puff volume (mL)          | 49.5 (0.15)               | 46.2 (0.15)       | 1.8 (2.13)               | 0.397       |
| Mean puff duration (sec)       | 1.4 (0.004)               | 1.3 (0.005)       | 0.04 (0.06)              | 0.529       |
| Time to peak (sec)             | 0.4 (0.002)               | 0.4 (0.002)       | -0.007 (0.02)            | 0.803       |
| Peak flow (mL/sec)             | 53.3 (0.16)               | 52.6 (0.15)       | 2.4 (2.47)               | 0.333       |
| Average flow (mL/sec)          | 36.6 (0.09)               | 37.9 (0.10)       | -0.2 (1.43)              | 0.905       |
| Total cigarette puff volume (mL)\(^b\) | 601.4 (7.30)              | 540.5 (7.01)      | 58.9 (29.49)             | 0.046       |
| Total time to finish cigarette (min) | 4.9 (0.07)                | 5.5 (0.07)        | -0.5 (0.23)              | 0.031       |
| Total cigarette puff rate (per min) | 3.3 (0.05)                | 2.7 (0.04)        | 0.6 (0.21)               | 0.006       |

\(^a\) Mean and standard error (SE) were estimated and compared using the random effects linear regression analysis.

\(^b\) Derived by adding the puff volumes for each cigarette.