Published in final edited form as:
J Psychiatr Res. 2013 July ; 47(7): 858–864. doi:10.1016/j.jpsychires.2013.03.012.

Temporal sequencing of nicotine dependence and bipolar disorder in the national epidemiologic survey on alcohol and related conditions (NESARC)

José M. Martínez-Ortega[a,b,*], **Benjamin I. Goldstein**[c], **Luis Gutiérrez-Rojas**[d], **Regina Sala**[a,e], **Shuai Wang**[a], and **Carlos Blanco**[a]

[a]New York State Psychiatric Institute, Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, NY, USA

[b]Department of Psychiatry and CTS-549 Research Group, Institute of Neurosciences, University of Granada, Granada, Spain

[c]Centre for Youth Bipolar Disorder, Department of Psychiatry, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

[d]Psychiatry Service, San Cecilio University Hospital, Granada, Spain

[e]Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College London, London, UK;

Abstract

Bipolar disorder (BD) and nicotine dependence (ND) often co-occur. However, the mechanisms underlying this association remain unclear. We aimed to examine, for the first time in a national and representative sample, the magnitude and direction of the temporal relationship between BD and ND; and to compare, among individuals with lifetime ND and BD, the sociodemographic and clinical characteristics of individuals whose onset of ND preceded the onset of BD (ND-prior) with those whose onset of ND followed the onset of BD (BD-prior). The sample included individuals with lifetime BD type I or ND (n=7958) from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, n=43093). Survival analyses and logistic regression models were computed to study the temporal association between ND and BD, and to compare ND-prior (n=135) and BD-prior (n=386) individuals. We found that ND predicted the onset of BD and BD also predicted the onset of ND. Furthermore, the risk of developing one disorder following the other one was greatest early in the course of illness. Most individuals with lifetime ND and BD were BD-prior (72.6%). BD-prior individuals had an earlier onset of BD and a higher number of manic episodes. By contrast, ND-prior individuals had an earlier onset of both daily smoking and ND, and an increased prevalence of alcohol use disorder. In conclusion, ND and BD predict the development of each other. The phenomenology and course of ND and BD varied significantly depending on which disorder had earlier onset.

[*]Corresponding author: José M. Martínez-Ortega, M.D., Ph.D., New York State Psychiatric Institute, Box 69, 1051 Riverside Drive, New York, NY 10032, USA. Tel: (212) 543 6533; Fax: (212) 543 6515; jmmartinezortega@ugr.es.
Dr Sala is currently employed by the Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College London, London, UK.

Keywords

bipolar disorder; nicotine dependence; age of onset; smoking; epidemiology

1. Introduction

Smoking and nicotine dependence (ND) continue to be the leading cause of preventable death worldwide, and they are more frequent among psychiatric patients. In particular, individuals with bipolar disorder (BD) as compared to the general population are more likely to have a lifetime history of smoking (Diaz et al., 2009; Gonzalez-Pinto et al., 1998; Lasser et al., 2000), current smoking (Diaz et al., 2009; Lasser et al., 2000), and ND (Grant et al., 2004), as well as lower rates of smoking cessation (Diaz et al., 2009; Lasser et al., 2000). ND has been associated with BD in epidemiological (Grant et al., 2004) and in clinical samples (Chandra et al., 2005). Because patients with BD are more likely to have medical illnesses often caused or exacerbated by cigarette smoking (Garcia-Portilla et al., 2010), a better knowledge of the reasons for the co-occurrence of ND and BD could help avoid premature deaths in this population.

The possible mechanisms underlying the association between ND and BD remain unclear and proposed hypotheses are largely based on the (better developed) literature on smoking and depression (Heffner et al., 2011). These authors (Heffner et al., 2011) put forth three possibilities: BD increases the risk of ND, ND increases the risk of BD, and BD and ND share common risk factors. First, BD may increase the risk of ND as the result of a self-medication approach (i.e. patients with BD may use nicotine to alleviate symptoms or treat side-effects). This mechanism is supported by the finding that acute nicotine use may relieve depressed mood (Berlin and Anthenelli, 2001; Kenny et al., 2000). Second, ND by itself could affect somatic or mental health adversely and hasten the onset of BD. In this line, chronic nicotine consumption may impair serotonin function (Malone et al., 2003) and enhance the risk of depression. Under these two hypotheses, the onset of ND and its temporal relationship with the onset of BD could be relevant. If BD increases the risk of ND in a self-medication manner, the onset of BD must be earlier than the onset of ND; whereas if ND contributes causally to BD, the onset of ND must occur first.

The goal of this study was two-fold: 1) to examine the magnitude and direction of the temporal relationship between BD and ND, controlling for sex and family history of substance use disorders, mood disorders or antisocial behavior, following the model of (Kuo et al., 2006) that is, examining the temporal relationship between the onset of alcohol dependence and the onset of major depressive disorder; and, 2) among individuals with lifetime ND and BD, to compare sociodemographic and clinical characteristics between individuals whose age of onset of ND preceded (ND-prior) or followed (BD-prior) the age of onset of BD, drawing on data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

2. Materials and methods

2.1 Sample

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) was a face-to-face survey conducted by the US Census Bureau under the direction of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 2001–2002 (Grant et al., 2003). The NESARC target population was the non-institutionalized, adult civilian population residing in the USA. The housing unit sampling frame was the US Bureau of the Census Supplementary Survey, which included the group quarters sampling frame derived from the

Census 2000 Group Quarters Inventory. Blacks, Hispanics, and young adults (ages 18–24 years) were oversampled to provide more precision on the estimates for these groups.

The research protocol, including informed consent procedures, was approved by the Census Bureau's Institutional Review Board and the US Office of Management and Budget. The final sample included 43,093 respondents, and the overall survey response rate was 81%. The NESARC sample was weighted to adjust for the probabilities of selection of: a sample housing unit or housing unit equivalent from the group quarters sampling frame, non-response at the household or person level, selection of one person per household, and oversampling of young adults. The weighted data were then adjusted for sociodemographic variables based on the 2000 Decennial Census. This study included all individuals with a lifetime history of BD-I or ND (n = 7958).

Although differences in rates of smoking or ND between BD type I (BD-I) and BD type II appear to be small (Grant et al., 2004; Waxmonsky et al., 2005), we focused exclusively on BD-I individuals to be consistent with most previous studies on smoking and BD (Gonzalez-Pinto et al., 1998; Heffner et al., 2012; Hughes et al., 1986; Itkin et al., 2001; Kreinin et al., 2012).

2.2 Measures

All diagnoses in the NESARC were made according to the DSM-IV (APA, 1994) criteria using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV version (AUDADIS-IV) (Grant et al., 2001), a valid and reliable fully structured diagnostic interview designed for use by non-clinicians (Williams et al., 1992). The test-retest reliability of AUDADIS-IV was good for BD-I ($\kappa = 0.65$) and excellent for drug diagnoses ($\kappa > 0.79$) (Canino et al., 1999; Grant et al., 2003). The good test-retest reliability of the AUDADIS-IV mood sections was comparable to that obtained with the computerized DSM-IV version of the Composite International Diagnostic Interview (CIDI) (any BD: $\kappa = 0.64$) (Wittchen et al., 1998). In addition, validity of BD-I diagnosis was assessed using the Mental Component, Social Functioning, Role Emotional Functioning, and Mental Health scores of the Short Form-12v2 (SF-12v2), a reliable and valid impairment measure in population surveys (Ware et al., 2002).

Sociodemographic characteristics included race/ethnicity, sex, age, urbanicity (urban vs. rural), level of education, individual income and marital status. Information was also collected on history of alcohol use disorder, drug use disorder, and depression and antisocial behavior among first-degree relatives of the respondent.

The age of onset of BD was considered to be when the respondent first met DSM-IV criteria for a manic or major depressive episode. Nicotine dependence was assessed separately via extensive items covering the DSM-IV criteria (APA, 1994) which require meeting three or more of seven criteria within a 12-month period. The age of onset of ND was considered when the respondent first met three or more of seven DSM-IV criteria for ND. The age of onset of daily smoking was determined by asking respondents about the age at which they first "started smoking every day". Finally, tobacco withdrawal symptoms were determined by asking respondents whether they experienced any of eight tobacco withdrawal symptoms (depression, sleep problems, difficulty concentrating, increased appetite, irritability or frustration, anxiety or nervousness, heart beating more slowly, restlessness) when attempting to quit smoking. Responses were summed for total withdrawal symptoms score (range 0–8; $\alpha = 0.93$) (Weinberger et al., 2010).

Individuals with lifetime ND and BD (n=573) were classified as having age of onset of ND earlier than their age of onset of BD (ND-prior; n=135) or later (BD-prior; n=386).

Individuals whose age of onset of ND was in the same year than age of onset of BD (n=52) were categorized as "concurrent" and excluded from analyses comparing ND-prior and BD-prior individuals, since we could not distinguish which one had an earlier onset.

2.3 Data analysis

Following the model of (Kuo et al., 2006), we used survival analyses to study the temporal association between ND and BD. We built three sets of Cox proportional hazard regression models including: 1) time-dependent diagnosis of each disorder, as well as family history of alcohol or drug use disorders, depression and antisocial behavior; 2) interactions of sex with time-dependent diagnosis and family history of the above psychiatric disorders; and 3) decay of the hazard modelled as logarithmic functions of time in order to test that the proportional hazard ratio (HR) held over time (Kuo et al., 2006).

We then computed weighted percentages and means to derive sociodemographic and clinical characteristics of BD respondents, ND-prior and BD-prior. Because the combined standard error of two means (or percents) is always equal or less than the sum of the standard errors of those two means, we conservatively consider two confidence intervals that share a boundary or do not overlap to be significantly different from one another (Agresti and Hartzel, 2000). Binary logistic regressions were conducted to compare the distribution of clinical variables between ND-prior and BD-prior respondents, adjusting for age and sex. We consider significant ORs those whose CI does not cross 1 (Agresti and Hartzel, 2000). All analyses, including point estimates, standard errors and 95% confidence intervals (CI) were performed using SUDAAN (Research, Triangle Institute 2004) to adjust for the complex design of the NESARC.

3. Results

Prevalence and age at onset of ND and BD, and the association of both conditions, are shown according to sex in Table 1. In the whole NESARC sample, males had a significantly higher prevalence of ND and a significantly earlier age of onset of both ND and BD than females ($P<0.001$). Among individuals with both ND and BD, there was a significantly higher proportion of ND-prior among males and a significantly higher proportion of BD-prior among females (P=0.03).

A series of Cox proportional hazard models predicting risk for ND are displayed in Table 2. Risk of developing ND was increased by the main effect of male sex, BD diagnosis and family history of drug use disorders. None of the five sex interaction terms included in the second model was significant. In the final model, after dropping the non-significant sex-interaction terms from the previous model, prior BD diagnosis increased the risk of developing ND, and the HR for the decay variable was significant, with a value of less than 1.

Models predicting risk for BD (Table 3) show an increased risk for BD associated with having prior ND onset and family history of depression or antisocial behavior. None of the five sex interaction terms included in the second model was significant. In the final model, ND-prior diagnosis strongly affected the risk of BD and the decay variable was also significant, with a value of less than 1.

Among individuals with lifetime ND and BD, 72.6% were BD-prior and 27.4% were ND-prior. Compared to ND-prior respondents, BD-prior respondents were significantly more likely to be never married (Table 4). BD-prior individuals had an earlier age of onset of first mood episode, first depressive episode and first manic episode, and a greater number of manic episodes (Table 4), but a later age of onset of both daily smoking and ND. On the

average, the transition time from daily smoking to ND was significantly longer for BD-prior individuals than for ND-prior ones (11.9 ± 0.7 vs. 4.4 ± 0.7 years, $P<0.001$).

Compared with BD-prior individuals, ND-prior individuals had a significantly greater proportion of lifetime alcohol use disorder. There were no differences in rates of hospitalization for BD or in family history of alcohol or drug use disorder, depression or antisocial behavior (Table 5).

4. Discussion

4.1 Main findings, strengths and limitations

In a large, nationally representative sample of US adults, survival analysis models showed that BD was associated with an increased risk of ND, of future onset of ND, and also, more strongly, with an increased risk of future BD. There were no significant sex interactions in the models, suggesting that these findings are similar among males and females. Moreover, the significant negative decay coefficients indicate that the risk of suffering one disorder after the other one decreased over time. When individuals with both BD and ND were compared according to which disorder had earlier onset, those who developed ND after the onset of BD (BD-prior) were more likely to have an earlier onset of BD and more manic episodes. By contrast, individuals who developed ND before the onset of BD (ND-prior) had an earlier onset of both daily smoking and ND, and increased odds of co-morbid alcohol use disorders. Finally, we found sex differences between ND-prior and BD-prior respondents (Table 1). The finding of a higher proportion of BD-prior among women could be related to the earlier onset of BD found among BD-prior respondents. However, the age of onset of BD in the total sample was significantly younger among men. The higher proportion of ND-prior among men could be attributed, at least in part, to an earlier onset of ND among men.

Some strengths of this study are the large sample size, the test-retest of the AUDADIS-IV for BD and drug diagnoses, and the consistency across analytic strategies which provide additional support for the validity of results. However, the potential limitations should be taken into consideration. First, the information regarding ND was based on self-report and not confirmed by objective methods. Second, diagnoses may be subject to recall bias. Third, consistent with DSM-IV, we considered the age of onset of BD as the age of onset of first manic or major depressive episode. However, some symptoms of BD, especially in youths, may be presented before the first full-threshold mood episode (Axelson et al., 2011). Finally, family history of BD or smoking was not collected in the NESARC.

4.2 Shared liability

In our sample, ND and BD predict the development of each other, indicating a bidirectional temporal relationship between BD and ND. One first possible explanation is that both disorders have shared or correlated risk factors, including genetic, physiological or environmental factors (Heffner et al., 2011). For example, genes encoding catechol-O-methyltransferase (COMT) or involving dopamine or serotonin systems may interact in predisposing for BD and substance use disorders (McEachin et al., 2010; Novak et al., 2010). In addition, brain structural and functional abnormalities shared between BD and ND may play an important role in the association of these two disorders. In particular, structural or dysfunctional abnormalities in the prefrontal cortex, which is involved in smoking and in ND (Chen et al., 2010; Janes et al., 2012), have been associated with the onset of mania and depression (Cummings, 1997). Aberrant amygdala activity has also been associated with BD (Cerullo et al., 2009) and ND (Mihov and Hurlemann, 2012). Finally, potentially shared environmental risk factors for BD and ND, including factors associated with alcohol and illicit drug use disorders and a history of childhood adversity, are likely to increase the risk

for both disorders (Heffner et al., 2011). Prospective and longitudinal studies are needed to identify biological or environmental risk factors for these co-morbid disorders.

4.3 Phenotypic causation

Our results also support, at least in part, the phenotypic causation hypothesis to explain the co-morbidity between ND and BD. The prediction from BD to ND and the fact that most individuals with lifetime ND and BD in our sample were BD-prior respondents would suggest a phenotypic causation role from BD to ND. At the same time, the higher hazard ratio found for ND preceding BD suggest a potential contribution of ND in increasing the risk of BD. Several mechanisms may explain these relationships.

First, BD might increase risk of ND in accordance with the self-medication hypothesis. (Weiss et al., 2004) investigated reasons for substance use in BD and found that two-thirds of patients reported improvement in at least one BD symptom as a result of substance use. In addition, among individuals with major depressive disorder, symptoms may increase the risk of smoking because of the ability of tobacco to inhibit monoamine oxidase A and B (Berlin and Anthenelli, 2001) or to stimulate the release of serotonin and dopamine (Kenny et al., 2000). However, some of our findings in BD-prior subjects such as the co-occurrence of an earlier onset of BD and a later onset of ND (with a latency of 11 years on average) and the longer transition from daily smoking to ND seem to contradict the self-medication hypothesis as a way to explain the association between ND and BD. Still, our results do not allow us to fully exclude the use of nicotine as a maladaptive attempt at self-medication among BD subjects, given that other aspects potentially related to nicotine use, such as the improvement of cognitive functioning (Heffner et al., 2011) or the reciprocal effect between nicotine and antipsychotic or antiepileptic medication, were not examined in the present study.

On the other hand, ND could hasten the onset of BD or increase BD symptoms. Chronic nicotine consumption can impair serotonin function, producing an imbalance between serotonin and dopamine, which may lead to enhanced consumption of nicotine and other drugs or a reduction of the brain inhibitory control systems (Olausson et al., 2002). Human postmortem studies have shown that smoking is associated with significant decreases in the concentrations of serotonin and 5-hydroxindolacetic acid (5-HIAA) in the hippocampus (Benwell et al., 1990). In addition, Malone et al. (2003) using a sample of depressed subjects without current substance abuse or alcohol dependence, found an inverse correlation between the number of cigarettes and two indices of serotonin function, cerebrospinal fluid 5-HIAA level and prolactin response to fenfluramine. Smoking may also increase the likelihood of emotional disturbances by reducing oxygen flow to the brain (Johnson et al., 2000).

In this mutual prediction between BD and ND, the risk of developing one disorder after the other one was greatest early in the course of illness. This fact underscores the opportunity for smoking prevention or cessation early in BD treatment, and early focus on mood symptoms among people with ND.

4.4 Age at onset and course of illness

BD-prior individuals in our sample were more likely to have a severe course of BD as indicated by an earlier onset and more manic episodes. By contrast, ND-prior individuals had an earlier onset of both daily smoking and ND, and an increased probability of co-morbid alcohol use disorders. These results support the hypothesis that differences in relative ages at onset of ND and BD in individuals with both conditions may affect the course of BD. Specifically, BD-prior individuals would have a more severe course of BD

with an earlier age of onset. According to our results, a higher number of manic episodes do not seem to be related to the onset of ND given the longer transition from daily smoking to ND among BD-prior compared to ND-prior subjects. Furthermore, we cannot exclude the role of BD in the development of ND since there may be cognitive, behavioral or psychosocial processes which we did not test and may have some influence, especially in a long term. On the other hand, ND-prior respondents would have less severe course of BD with an older age of onset, but more severe ND with earlier age of onset and a higher vulnerability for co-morbid alcohol use disorder. Our results are in line with those of (DelBello et al., 1999), who found that the age of onset of BD was older in patients with a history of alcohol dependence than in patients without such history. *An older age of onset of BD has been associated with lower familial rates of BD (*DelBello et al., 1999). ND may precipitate the onset of BD in less predisposed individuals whose genetic liability might have been otherwise insufficient to precipitate the symptoms of BD. Unfortunately, it is not possible to know whether there is difference in family history of BD between ND-prior and BD-prior since the NESARC does not contain information on family history of BD. Furthermore, since alcohol seems to predict tobacco use more strongly than vice versa (Jackson et al., 2002), the earlier onset of ND among ND-prior in our sample may be explained, at least in part, by the higher proportion of alcohol use disorder in these subjects. An earlier onset of ND should alert health care professionals as to the development of later psychopathology or other substance use disorders, particularly alcohol use disorders.

4.5 Conclusion

In conclusion, our findings suggest a strong association between ND and BD in both sexes. Although our results are consistent with both phenotypic causation and the existence of a shared underlying liability for the onset of both disorders, perhaps neither the phenotypic causation nor the correlated cause hypothesis can, by itself, explain this co-morbidity. The mechanisms responsible for co-morbidity of ND and BD could vary over individuals and families and represent etiologically distinct subgroups. A better understanding of the brain pathophysiology of ND may help us to better understand the brain pathophysiology of BD (Diaz et al., 2009). There is a significant need for research to afford better knowledge of such co-morbidity and to identify the best approaches toward facilitating long-term smoking abstinence for smokers with BD, thereby reducing the prevalence and consequences of this hazardous addiction (Heffner et al., 2011).

Acknowledgments

The National Epidemiologic Survey on Alcohol and Related Conditions was sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). We thank the New York State Psychiatric Institute and the University of Granada.

The authors thank Professor Manuel Gurpegui, of the University of Granada, for suggesting the possible focus of research to JMMO and for critical comments of the manuscript.

References

Agresti A, Hartzel J. Strategies for comparing treatments on a binary response with multi-centre data. Statistics in medicine. 2000; 19:1115–39. [PubMed: 10790684]

APA. Diagnostic and statistical manual of mental disorders. 4. American Psychiatric Association; Washington, DC: 1994.

Axelson DA, Birmaher B, Strober MA, Goldstein BI, Ha W, Gill MK, et al. Course of subthreshold bipolar disorder in youth: diagnostic progression from bipolar disorder not otherwise specified. J Am Acad Child Adolesc Psychiatry. 2011; 50:1001–16. e3. [PubMed: 21961775]

Benwell ME, Balfour DJ, Anderson JM. Smoking-associated changes in the serotonergic systems of discrete regions of human brain. Psychopharmacology (Berl). 1990; 102:68–72. [PubMed: 1697418]

Berlin I, Anthenelli RM. Monoamine oxidases and tobacco smoking. Int J Neuropsychopharmacol. 2001; 4:33–42. [PubMed: 11343627]

Canino G, Bravo M, Ramirez R, Febo VE, Rubio-Stipec M, Fernandez RL, et al. The Spanish Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS): reliability and concordance with clinical diagnoses in a Hispanic population. J Stud Alcohol. 1999; 60:790–9. [PubMed: 10606491]

Cerullo MA, Adler CM, Delbello MP, Strakowski SM. The functional neuroanatomy of bipolar disorder. Int Rev Psychiatry. 2009; 21:314–22. [PubMed: 20374146]

Cummings JL. Neuropsychiatric manifestations of right hemisphere lesions. Brain Lang. 1997; 57:22–37. [PubMed: 9126405]

Chandra PS, Carey MP, Carey KB, Jairam KR, Girish NS, Rudresh HP. Prevalence and correlates of tobacco use and nicotine dependence among psychiatric patients in India. Addict Behav. 2005; 30:1290–9. [PubMed: 16022927]

Chen TY, Dragomir A, Zhang D, Akay Y, Akay M. Prefrontal cortex deletion affects the dopaminergic neural firing complexity in nicotine-treated ventral tegmental area. Conf Proc IEEE Eng Med Biol Soc. 2010; 2010:4526–9. [PubMed: 21095787]

DelBello MP, Strakowski SM, Sax KW, McElroy SL, Keck PE Jr, West SA, et al. Familial rates of affective and substance use disorders in patients with first-episode mania. J Affect Disord. 1999; 56:55–60. [PubMed: 10626780]

Diaz FJ, James D, Botts S, Maw L, Susce MT, de Leon J. Tobacco smoking behaviors in bipolar disorder: a comparison of the general population, schizophrenia, and major depression. Bipolar Disord. 2009; 11:154–65. [PubMed: 19267698]

Garcia-Portilla MP, Saiz PA, Benabarre A, Florez G, Bascaran MT, Diaz EM, et al. Impact of substance use on the physical health of patients with bipolar disorder. Acta Psychiatr Scand. 2010; 121:437–45. [PubMed: 19895620]

Gonzalez-Pinto A, Gutierrez M, Ezcurra J, Aizpuru F, Mosquera F, Lopez P, et al. Tobacco smoking and bipolar disorder. J Clin Psychiatry. 1998; 59:225–8. [PubMed: 9632031]

Grant, BF.; Dawson, DA.; Hasin, DS. The alcohol use disorder and associated disabilities interview schedule-DSM-IV version. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism; 2001.

Grant BF, Dawson DA, Stinson FS, Chou PS, Kay W, Pickering R. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. Drug Alcohol Depend. 2003; 71:7–16. [PubMed: 12821201]

Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry. 2004; 61:1107–15. [PubMed: 15520358]

Heffner JL, DelBello MP, Anthenelli RM, Fleck DE, Adler CM, Strakowski SM. Cigarette smoking and its relationship to mood disorder symptoms and co-occurring alcohol and cannabis use disorders following first hospitalization for bipolar disorder. Bipolar Disord. 2012; 14:99–108. [PubMed: 22329477]

Heffner JL, Strawn JR, DelBello MP, Strakowski SM, Anthenelli RM. The co-occurrence of cigarette smoking and bipolar disorder: phenomenology and treatment considerations. Bipolar Disord. 2011; 13:439–53. [PubMed: 22017214]

Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA. Prevalence of smoking among psychiatric outpatients. Am J Psychiatry. 1986; 143:993–7. [PubMed: 3487983]

Itkin O, Nemets B, Einat H. Smoking habits in bipolar and schizophrenic outpatients in southern Israel. J Clin Psychiatry. 2001; 62:269–72. [PubMed: 11379841]

Jackson KM, Sher KJ, Cooper ML, Wood PK. Adolescent alcohol and tobacco use: onset, persistence and trajectories of use across two samples. Addiction. 2002; 97:517–31. [PubMed: 12033653]

Janes AC, Nickerson LD, Frederick B, Kaufman MJ. Prefrontal and limbic resting state brain network functional connectivity differs between nicotine-dependent smokers and non-smoking controls. Drug Alcohol Depend. 2012; 125:252–9. [PubMed: 22459914]

Johnson JG, Cohen P, Pine DS, Klein DF, Kasen S, Brook JS. Association between cigarette smoking and anxiety disorders during adolescence and early adulthood. JAMA. 2000; 284:2348–51. [PubMed: 11066185]

Kenny PJ, File SE, Neal MJ. Evidence for a complex influence of nicotinic acetylcholine receptors on hippocampal serotonin release. J Neurochem. 2000; 75:2409–14. [PubMed: 11080192]

Kreinin A, Novitski D, Rabinowitz D, Weizman A, Grinshpoon A. Association between tobacco smoking and bipolar affective disorder: clinical, epidemiological, cross-sectional, retrospective study in outpatients. Compr Psychiatry. 2012; 53:269–74. [PubMed: 21664608]

Kuo PH, Gardner CO, Kendler KS, Prescott CA. The temporal relationship of the onsets of alcohol dependence and major depression: using a genetically informative study design. Psychol Med. 2006; 36:1153–62. [PubMed: 16734951]

Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: A population-based prevalence study. JAMA. 2000; 284:2606–10. [PubMed: 11086367]

Malone KM, Waternaux C, Haas GL, Cooper TB, Li S, Mann JJ. Cigarette smoking, suicidal behavior, and serotonin function in major psychiatric disorders. Am J Psychiatry. 2003; 160:773–9. [PubMed: 12668368]

McEachin RC, Saccone NL, Saccone SF, Kleyman-Smith YD, Kar T, Kare RK, et al. Modeling complex genetic and environmental influences on comorbid bipolar disorder with tobacco use disorder. BMC Med Genet. 2010; 11:14. [PubMed: 20102619]

Mihov Y, Hurlemann R. Altered amygdala function in nicotine addiction: Insights from human neuroimaging studies. Neuropsychologia. 2012; 50:1719–29. [PubMed: 22575084]

Novak G, Zai CC, Mirkhani M, Shaikh S, Vincent JB, Meltzer H, et al. Replicated association of the NR4A3 gene with smoking behaviour in schizophrenia and in bipolar disorder. Genes Brain Behav. 2010; 9:910–7. [PubMed: 20659174]

Olausson P, Engel JA, Soderpalm B. Involvement of serotonin in nicotine dependence: processes relevant to positive and negative regulation of drug intake. Pharmacol Biochem Behav. 2002; 71:757–71. [PubMed: 11888567]

Research, Triangle Institute. Software for Survey Data Analysis (SUDAAN) Version 9.0. Research Triangle Institute; Research Triangle Park: 2004.

Ware, JE.; Kosinski, M.; Turner-Bowker, DM.; Gandek, B. Incorporated Q, Lab NEMCHHA. How to score version 2 of the SF-12 Health Survey. Quality Metrics; Lincoln: 2002.

Waxmonsky JA, Thomas MR, Miklowitz DJ, Allen MH, Wisniewski SR, Zhang H, et al. Prevalence and correlates of tobacco use in bipolar disorder: data from the first 2000 participants in the Systematic Treatment Enhancement Program. Gen Hosp Psychiatry. 2005; 27:321–8. [PubMed: 16168792]

Weinberger AH, Desai RA, McKee SA. Nicotine withdrawal in U.S. smokers with current mood, anxiety, alcohol use, and substance use disorders. Drug Alcohol Depend. 2010; 108:7–12. [PubMed: 20006451]

Weiss RD, Kolodziej M, Griffin ML, Najavits LM, Jacobson LM, Greenfield SF. Substance use and perceived symptom improvement among patients with bipolar disorder and substance dependence. J Affect Disord. 2004; 79:279–83. [PubMed: 15023508]

Williams JB, Gibbon M, First MB, Spitzer RL, Davies M, Borus J, et al. The Structured Clinical Interview for DSM-III-R (SCID). II. Multisite test-retest reliability. Arch Gen Psychiatry. 1992; 49:630–6. [PubMed: 1637253]

Wittchen HU, Lachner G, Wunderlich U, Pfister H. Test-retest reliability of the computerized DSM-IV version of the Munich-Composite International Diagnostic Interview (M-CIDI). Soc Psychiatry Psychiatr Epidemiol. 1998; 33:568–78. [PubMed: 9803825]

Table 1

Prevalence and age at onset of nicotine dependence and bipolar disorder and the association of both conditions

	Males	Females	t/χ^2	df	p-value
NESARC sample (n = 43.093)	18518 (47.9%)	24575 (52.1%)			
Age of onset of ND [a]	30.3 (0.3)	31.9 (0.3)	−4.07		<0.001
Age of onset of first mood episode [a]	27.9 (0.3)	29.6 (0.2)	−4.43		<0.001
ND prevalence	3404 (20.0%)	3533 (15.6%)	63.39	1	<0.001
BD-I prevalence	579 (3.2%)	832 (3.4%)	1.66	1	0.202
Co-morbid status					
ND only	3126 (18.5%)	3210 (14.2%)	23.53	3	<0.001
BD-I only	301 (1.6%)	509 (2.05%)			
Co-morbidity of ND and BD	278 (1.5%)	323 (1.4%)			
Co-morbid sample (n = 573) [b]					
BD-prior	165 (59.9%)	221 (72.0%)	3.73	2	0.029
ND-prior	75 (27.1%)	60 (22.4%)			
Concurrent	29 (13.0%)	23 (5.6%)			

ND = nicotine dependence; BD-I = bipolar disorder type I; ND-prior = smokers whose age of onset of ND was before than their age of onset of first mood episode; BD-prior = smokers whose age of onset of ND was after than their age of onset of first mood episode; Co-morbid sample = ND + BD-I; Concurrent = age of onset of ND in the same year as age of onset of first mood episode.

[a] Mean age at first onset, and standard error (SE) in parentheses

[b] Temporal relation of ND and BD

Table 2

Hazard ratio (and 95% confidence interval) for nicotine dependence among individuals with prior bipolar disorder (n=1393) controlling for sex and family history of drug use, depression and antisocial behavior

	HR (95% CI)		
Predictors	**Test for main effect**	**Test for sex interaction**	**Final model with decay**
Sex [a]	**1.5 (1.2–1.8)** ***	1.30 (0.8–2.1)	1.2 (0.9–1.5)
BD_time-dependent	**1.5 (1.2–1.8)** **	1.32 (1.0–1.7)	**2.8 (2.1–3.8)** ***
Drug use family history	**1.3 (1.1–1.6)** *	1.34 (0.9–1.8)	0.9 (0.7–1.1)
Alcohol use family history	1.1 (0.9–1.4)	1.10 (0.8–1.6)	**0.7 (0.5–0.8)** **
Depression family history	1.0 (0.8–1.3)	0.96 (0.7–1.3)	1.1 (0.9–1.4)
Antisocial behavior family history	1.1 (0.9–1.3)	1.09 (0.8–1.5)	1.2 (0.9–1.4)
Sex x BD_time-dependent		1.20 (0.8–1.8)	
Sex x Drug use family history		0.96 (0.6–1.4)	
Sex x Alcohol use family history		1.02 (0.6–1.6)	
Sex x Depression family history		1.11 (0.7–1.7)	
Sex x Antisocial behavior family history		0.96 (0.6–1.5)	
Decay by year [b]			**0.86 (0.8–0.9)** ***

HR = hazard ratio; CI = confidence interval.

[a] Male = 1, female = 2

[b] Decay as log (ND - BD age of onset)

* p<0.05,

** p<0.01,

*** p<0.001

Table 3

Hazard ratio (and 95% confidence interval) for bipolar disorder among individuals with prior nicotine dependence (n=6565) controlled for sex and family history of drug use, depression and antisocial behavior

	HR (95% CI)		
Predictors	**Test for main effect**	**Test for sex interaction**	**Final model with decay**
Sex [a]	1.1 (0.9–1.3)	0.9 (0.6–1.4)	0.8 (0.6–1.0)
ND_time-dependent	**1.7 (1.3–2.2)** ***	**1.4 (1.01–2.1)** *	**25. 6 (13.0–50.4)** ***
Drug use family history	1.2 (0.9–1.6)	1.3 (0.9–1.8)	1.1 (0.8–1.5)
Alcohol use family history	1.1 (0.9–1.4)	1.2 (0.9–1.7)	0.9 (0.7–1.4)
Depression family history	**2.5 (1.9–3.2)** ***	**2.3 (1.6–3.2)** ***	1.2 (0.9–1.7)
Antisocial behavior family history	**1.7 (1.4–2.2)** ***	**1.6 (1.1–2.2)** **	1.1 (0.8–1.6)
Sex x ND_time-dependent		1.4 (0.9–2.2)	
Sex x Drug use family history		0.9 (0.5–1.5)	
Sex x Alcohol use family history		0.9 (0.6–1.4)	
Sex x Depression family history		1.2 (0.7–1.8)	
Sex x Antisocial behavior family history		1.2 (0.7–1.9)	
Decay by year [b]			**0.79 (0.7–0.8)** ***

HR = hazard ratio; CI = confidence interval.

[a] Male = 1, female = 2

[b] Decay as log (BD - ND age of onset)

* p<0.05,

** p<0.01,

*** p<0.001

Table 4

Sociodemographic and clinical differences between bipolar disorder individuals whose onset of nicotine dependence was before their onset of bipolar disorder (ND-prior) and those whose onset of bipolar disorder was before their onset of nicotine dependence (BD-prior)

	ND-prior (n = 135)	**BD-prior (n = 386)**		
	% (SE)	**% (SE)**	**OR[a]**	**95 % CI**
Sex: male	56.5 (5.1)	47.1 (2.9)	1.4	0.9–2.4
Age				
18–29	27.9 (4.3)	36.6 (2.9)	1.0	1.0–1.0
30–44	38.6 (4.6)	35.9 (3.1)	1.4	0.8–2.5
≥45	33.5 (4.7)	27.5 (2.6)	1.6	0.9–2.9
Race/ethnicity				
White non Hispanic	82.2 (4.3)	77.4 (2.8)	1.0	1.0–1.0
Other	17.8 (4.3)	22.6 (2.8)	0.7	0.4–1.4
Education				
≤ High school	60.7 (4.8)	53.3 (3.4)	1.4	0.8–2.3
≥ College	39.3 (4.8)	46.7 (3.4)	1.0	1.0–1.0
Marital status				
Married	58.3 (4.4)	48.0 (3.2)	1.0	1.0–1.0
Widowed/divorced/separated	22.2 (4.2)	24.1 (2.6)	0.8	0.4–1.3
Never married	**19.6 (3.7)**	**27.9 (2.5)**	**0.6**	**0.3–0.9**
Personal Income				
$0–19,999	54.4 (4.6)	65.75 (3.2)	1.0	1.0–1.0
$20,000–34,999	25.8 (4.0)	19.7 (2.4)	1.6	0.9–2.6
≥$35,000	19.8 (4.0)	14.5 (2.1)	1.7	0.8–3.3
Urbanicity: rural	20.5 (4.6)	23.4 (3.5)	0.8	0.5–1.5
	Mean (SE)	Mean (SE)	*t*-test	p-value
Age of onset of first mood episode, years	**29.7 (1.3)**	**18.2 (0.5)**	**8.6**	**<0.001**
Age of first depressive episode, years	**30.4 (1.6)**	**21.4 (0.7)**	**5.1**	**<0.001**
Age of first manic episode, years	**30.1 (1.1)**	**21.6 (0.6)**	**7.0**	**<0.001**
Number of lifetime depression phases	6.1 (1.4)	9.5 (1.1)	−1.9	0.061
Number of lifetime manic phases	**4.2 (0.8)**	**8.4 (1.0)**	**−3.2**	**0.002**
Age of onset of first full cigarette smoked, years	14.2 (0.4)	14.5 (0.2)	−0.6	0.555
Age of onset of daily smoking, years	**16.05 (0.4)**	**17.5 (0.3)**	**−3.2**	**0.002**
Age of onset of nicotine dependence, years	**20.6 (0.7)**	**29.5 (0.7)**	**−9.8**	**<0.001**
Number cigarettes smoked per day	22.7 (1.4)	20.0 (0.7)	1.7	0.091
Number of withdrawal symptoms	4.2 (0.2)	4.4 (0.1)	−0.7	0.456
SF-12				
Mental Component Summary Score	44.5 (1.3)	41.7 (0.8)	1.8	0.072
Physical Disability Scale Score	48.7 (1.2)	48.4 (0.7)	0.2	0.847

BD-I = bipolar disorder type I; ND-prior = smokers whose age of onset of ND was before their age of onset of first mood episode; BD-prior = smokers whose age of onset of ND was after their age of onset of first mood episode. OR = odds ratio; CI = confidence interval; SE = standard error.

[a]Patients whose age of onset of ND was in the same year of age of onset as first mood episode were excluded from analysis.

Table 5

Personal and familial psychiatric history between bipolar disorder individuals whose onset of nicotine dependence was before their onset of bipolar disorder (ND-prior) and those whose onset of bipolar disorder was before their onset of nicotine dependence (BD-prior)

	ND-prior (n = 135)	BD-prior (n = 386)		
	% (SE)	% (SE)	OR[b]	95 % CI
Any Axis I diagnosis [a]	94.4 (2.2)	92.7 (1.5)	1.3	0.5–3.3
Any lifetime anxiety disorder	61.3 (5.0)	61.2 (2.9)	1.0	0.6–1.7
Any lifetime alcohol use disorder	**87.0 (3.2)**	**75.4 (2.5)**	**2.1**	**1.1–4.2**
Any lifetime drug use disorder	62.0 (4.7)	55.0 (3.2)	1.4	0.8–2.3
Any personality disorder	70.7 (4.9)	70.3 (2.6)	1.0	0.6–1.7
Any hospitalization	31.2 (4.6)	35.7 (3.1)	0.7	0.4–1.3
Family history				
Alcohol use disorder	67.9 (4.7)	64.7 (2.7)	1.1	0.7–1.8
Drug use disorder	45.3 (5.8)	43.4 (3.1)	1.1	0.6–1.9
Depression	69.6 (5.1)	74.1 (2.5)	0.8	0.5–1.4
Antisocial behavior	52.6 (5.1)	54.1 (2.7)	1.0	0.6–1.5

BD-I = bipolar disorder type I; ND-prior = smokers whose age of onset of ND was before their age of onset of first mood episode; BD-prior = smokers whose age of onset of ND was after their age of onset of first mood episode; OR = odds ratio; CI = confidence interval; SE = standard error.

[a] Excluding BD-I and ND.

[b] Adjusted for sex and age. Patients whose age of onset of ND was in the same year of age of onset as first mood episode were excluded from analysis.