Factors Associated With Temporal Priority in Comorbid Bipolar I Disorder and Alcohol Use Disorders: Results From the National Epidemiologic Survey on Alcohol and Related Conditions

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Objective: To compare illness characteristics, comorbidities, treatment utilization, and family history among individuals with comorbid bipolar I disorder and alcohol use disorders (AUD) based on temporal priority of onset.

Method: The 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions identified respondents with lifetime comorbid bipolar I disorder and AUD for whom AUD were antecedent (Alcohol First; N = 311), the onset of the 2 conditions occurred in the same year (Same Year; N = 113), or bipolar I disorder was antecedent (Bipolar First; N = 233). Diagnoses were generated using the National Institute on Alcohol Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV Version. This study examined between-group differences in bipolar I– and AUD-related variables.

Results: Bipolar First respondents were most likely to experience prolonged manic episodes. There were no differences in the 12-month prevalence of bipolar I disorder among respondents with prior history of bipolar I disorder. The 12-month prevalence of AUD among respondents with prior history of AUD was lower among Alcohol First respondents compared to Same Year or Bipolar First respondents. Same Year respondents were most likely to seek AUD treatment and reported comparatively short latency between onset and treatment of both bipolar I disorder and AUD. The prevalence of family history of comorbid depression and AUD was greatest among Same Year respondents. Same Year respondents also showed the lowest prevalence of anxiety disorders. Overall psychosocial functioning was similar across groups.

Conclusion: Temporal priority in comorbid bipolar I disorder and AUD is associated with several significant between-group differences in features of bipolar I disorder and AUD severity, treatment utilization, other comorbidities, and family history. Same-year onset of bipolar I disorder and AUD may be a marker of a specific subtype of bipolar I–AUD comorbidity. Potential implications of these findings are discussed.

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More than 80 years ago, Kraepelin[1] observed a high prevalence of alcoholism among his manic-depressive patients. Recently, the results of 3 independent epidemiologic community studies indicate that the prevalence of comorbid alcohol use disorders (AUD; i.e., alcohol abuse or dependence) among individuals with bipolar disorder is greater than that of any other drug use disorders and that alcohol is more strongly associated with bipolar disorder than with any other mood or anxiety disorder.[2–4] Data from clinical samples confirm that alcohol is the most commonly abused drug among individuals with bipolar disorder.[5] The deleterious effect of AUD on the course, treatment, and outcome of bipolar disorder has been shown repeatedly.[6–9] When AUD occur in bipolar disorder, recovery is delayed, relapse is hastened, symptoms are greater in number and persist between episodes, and disability and mortality are increased.[6]

Less clear, however, is the significance of the temporal priority (i.e., order of onset) of these disorders. To our knowledge, 3 previous studies have reported demographic and clinical differences between groups of individuals with antecedent bipolar disorder as compared to antecedent AUD.[8,10,11] Winokur and colleagues[8] conducted a 5-year follow-up study that included 70 subjects with comorbid bipolar disorder and AUD. Subjects with antecedent AUD experienced significantly fewer mood episodes during follow-up, and demonstrated significantly longer

median time to mood episode relapse, than subjects with antecedent bipolar disorder. Subjects with antecedent bipolar disorder were more likely than those with antecedent AUD to remain unrecovered from the index manic episode at 5-year follow-up. Less than 10% of comorbid bipolar disorder–AUD subjects demonstrated current alcoholism at 5-year follow-up. There were no significant differences in family history of bipolar disorder, unipolar depression, or alcoholism between comorbid subjects with antecedent bipolar disorder versus antecedent AUD. However, there was a signal that comorbidity itself may be familial, as relatives of comorbid probands were more likely to have comorbid bipolar disorder–AUD themselves than relatives of bipolar-only probands.

Feinman and Dunner[10] compared subjects with bipolar disorder alone (including bipolar I, bipolar II, bipolar disorder not otherwise specified, and cyclothymia) to comorbid subjects with antecedent bipolar disorder and comorbid subjects with antecedent substance use disorders (SUD). Positive family history of AUD was most common among comorbid subjects with antecedent bipolar disorder. Clinically, comorbid subjects with antecedent SUD were less likely to evidence rapid cycling, although prevalence of panic was similar.

Finally, a recent study by Strakowski and colleagues[11] examined the impact of temporal priority on the courses of illness of patients with comorbid bipolar I disorder and AUD following a first hospitalization for mania. In that study, comorbid patients with antecedent bipolar I disorder were more severely affected in terms of both bipolar I disorder and AUD during follow-up of up to 5 years' duration. Specifically, there was prolonged time to recovery and more time spent in affective episodes.

Importantly, previous studies of temporal priority in comorbid bipolar disorder–AUD have been derived from clinically ascertained samples and may not be representative of bipolar disorder–AUD in general. Therefore, a large-scale population study of this topic is needed to mitigate the known selection biases of clinical or treatment samples[12] and to yield results that can be more readily generalized to individuals with bipolar disorder in the community. The overarching rationale for the hypotheses of this study, similar to that articulated by Winokur and colleagues,[8] is that the secondary condition may not have manifested in the absence of the antecedent condition. The present study examined the following hypotheses: (1) respondents with antecedent bipolar I disorder (Bipolar First) and respondents with onset of both bipolar I disorder and AUD in the same year (Same Year) would report greater bipolar I disorder severity (as determined by 12-month prevalence of bipolar I disorder, mood episode frequency, rapid cycling, prolonged mood episodes, and bipolar I–related health service utilization) than respondents with antecedent AUD (Alcohol First), (2) Alcohol First respondents would report greater AUD severity than Same Year or Bipolar First respondents (as determined by a higher 12-month prevalence of AUD and more AUD-related service utilization), and (3) Alcohol First individuals would report greater prevalence of a family history of alcoholism, lower prevalence of a family history of depression, and similar prevalence of familial comorbidity as compared to Same Year or Bipolar First respondents.

We did not include primary hypotheses regarding anxiety disorders or personality disorders as there is minimal evidence that could inform such hypotheses. Nonetheless, we performed exploratory analyses to determine any differences in the prevalence of these conditions that commonly co-occur in bipolar I disorder.

METHOD

Subjects

Subjects were identified from among the respondents of the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Respondents with lifetime bipolar I disorder and lifetime AUD for whom age at onset of both conditions was available (N = 657) were included in the present study and were divided into 3 groups for the purpose of analyses: respondents with antecedent AUD (Alcohol First; N = 311), respondents with onset of both bipolar I disorder and AUD in the same year (Same Year; N = 113), and respondents with antecedent bipolar I disorder (Bipolar First; N = 233). The NESARC is a representative sample of the United States conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). A detailed description of the NESARC has been published elsewhere.[4] In brief, 43,093 noninstitutionalized civilian respondents, 18 years and older, completed face-to-face computer-assisted personal interviews. The overall survey response rate was 81%.

Assessment

Approximately 1800 lay interviewers with an average of 5 years' related experience administered the NESARC using laptop computer–assisted software. Interviewers completed 10 days of centralized, standardized training sessions. The NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV Version (AUDADIS-IV)[13] was used to generate the diagnoses presented in this report. The AUDADIS-IV diagnoses of personality disorders, SUD,[14] and mood and anxiety disorders[4,15] have demonstrated reliability and validity. Reliability of the bipolar I disorder diagnosis ($\kappa = 0.59$) is fair,[16] while the reliability for lifetime AUD ($\kappa = 0.70$) is good.[15] Age at onset of bipolar I disorder (i.e., age at first manic/mixed episode) and AUD, lifetime number of mood episodes, age at first treatment of bipolar I disorder and AUD, types of treatment, and demographic

Table 1. Demographic Characteristics of Individuals With Lifetime Comorbid Bipolar I Disorder and Alcohol Use Disorders (AUD) by Temporal Priority

	Antecedent AUD (N = 311)		Same Year (N = 113)		Antecedent Bipolar I Disorder (N = 233)		Statistics		
Characteristic	N	%	N	%	N	%	Test Result	df	p
Male	168	54	60	53	137	59	$\chi^2 = 1.7$	2	.46
Caucasian	244	79	95	84	197	85	$\chi^2 = 3.9$	2	.15
Cohabiting/married	134	43	45	40	88	38	$\chi^2 = 1.6$	2	.45
	Mean	SD	Mean	SD	Mean	SD			
Age, y	41.8	12.7	32.9[a]	13.1	35.2[a]	13.1	F = 28.2	2,654	< .001
Annual personal income, $1000s	22.5	21.6	18.7	17.5	22.0	25.6	F = 1.3	2,654	.28

[a]$p < .05$ vs. antecedent AUD.

variables were all determined by self-report data from the AUDADIS-IV. Rapid-cycling status was determined by the mean number of mood episodes per year (≥ 4) since the onset of bipolar I disorder.

The NESARC also includes among its measures the Short-Form-12v2 (SF-12v2),[17] a reliable and valid measure of generic quality of life used in large population surveys that yields 10 component and profile scores assessing various dimensions of physical and mental disability and impairment. The present study focused on 4 SF-12v2 health survey mental disability scores: the mental component summary score; the social functioning score, reflecting limitations in social functioning due to physical or emotional problems; the role emotional function score, measuring role impairment due to emotional problems; and the mental health score, reflecting general mental health functioning. Standard norm-based scoring techniques were used to transform each score to achieve a mean of 50 and standard deviation of 10 in the general population, with higher scores indicating better functioning.

The AUDADIS-IV explicitly addresses the temporal contiguity of manic episodes with substance use, when present. Bipolar I disorder was classified as independent of substance use in the following circumstances: (1) the respondent abstained from alcohol and drug use in the 12 months preceding the assessment, (2) the episode(s) did not occur in the context of alcohol or drug intoxication or withdrawal, (3) the episode(s) occurred before alcohol or drug intoxication or withdrawal, or (4) the episode(s) began after alcohol or drug intoxication or withdrawal, but persisted for more than 1 month after the cessation of alcohol or drug intoxication or withdrawal. Only cases in which mania occurred independently of substance use were included in the bipolar I group analyses.

One-way analysis of variance was used to compare differences between groups on dimensional measures, and χ^2 analyses were computed to detect differences on categorical measures. Weighting procedures were not used since this study is not intended to provide population prevalence estimates for any of the diagnoses described herein. These estimates have been previously reported.[4,14,16]

RESULTS

Sociodemographic Characteristics

As shown in Table 1, the 3 groups were significantly different from one another in age only ($F = 28.2$, df = 2,654; $p < .001$), with an older mean age among the Alcohol First group as compared to either the Same Year ($p < .05$) or Bipolar First ($p < .05$) groups by post hoc least significant difference test. Therefore, subsequent analyses involving clinical variables controlled for age. The groups were not significantly different from one another in terms of gender, ethnicity, marital status, or annual personal income.

Bipolar Disorder Severity

Clinical characteristics of the 3 groups of respondents included in the present study are found in Table 2. There were no significant between-group differences in the prevalence of rapid cycling ($\chi^2 = 0.4$, df = 2, $p = .80$) or prolonged depression episodes (> 12 months; $\chi^2 = 0.9$, df = 2, $p = .65$). However, Bipolar First respondents were more likely to endorse a history of a prolonged (> 6 months) manic episode (42%) as compared to Alcohol First respondents (30%; $\chi^2 = 7.6$, df = 1, $p = .006$) and Same Year respondents (28%; $\chi^2 = 5.8$, df = 1, $p = .02$). Using post hoc least significant difference test, Bipolar First respondents reported a greater mean number of lifetime mood episodes (mean = 22.9, SD = 39.3) than either Alcohol First respondents (mean = 11.7, SD = 22.5; $p < .05$) or Same Year respondents (mean = 9.6, SD = 19.4; $p < .05$). However, the mean number of mood episodes per year did not differ significantly between groups ($F = 1.1$, df = 2,535; $p = .58$). The persistence of bipolar I disorder was also examined as a marker of severity. Five hundred seventy respondents reported onset of both bipolar I disorder and AUD prior to the past year. Twelve-month prevalence of bipolar I disorder (i.e., a major depressive, mixed, or manic episode) among these respondents is reported in Table 3. There was no significant between-group difference in the 12-month prevalence of bipolar I disorder ($\chi^2 = 1.9$, df = 2, $p = .39$). There was no significant between-group difference in proportion of re-

Table 2. Clinical Characteristics of Individuals With Lifetime Comorbid Bipolar I Disorder and Alcohol Use Disorders (AUD) by Temporal Priority

	Antecedent AUD (N = 311)		Same Year (N = 113)		Antecedent Bipolar I Disorder (N = 233)		Statistics		
Characteristic	N	%	N	%	N	%	Test Result	df	p
Rapid cycling	24	8	10	9	19	8	$\chi^2 = 0.4$	2	.80
Lifetime manic episode > 6 mo	94	30	32	28	97	42[a,b]	$\chi^2 = 9.7$	2	.008
Lifetime depression episode > 12 mo	102	33	32	28	71	31	$\chi^2 = 0.9$	2	.65
Lifetime anxiety disorder	175	56	39	35[a]	111	48	$\chi^2 = 16.2$	2	< .001
Personality disorder	216	70	73	65	176	76	$\chi^2 = 4.9$	2	.09
Sought AUD treatment	94	30	47	42[a]	69	30[b]	$\chi^2 = 5.8$	2	.05
Sought bipolar I disorder treatment	156	50	62	55	115	50	$\chi^2 = 1.0$	2	.61
Parental alcoholism	155	50	63	56	117	50	$\chi^2 = 1.2$	2	.54
Parental depression	178	57	77	68	135	58	$\chi^2 = 4.4$	2	.11
Parental comorbidity	83	27	44	39[a]	65	28[b]	$\chi^2 = 6.3$	2	.04
	Mean	SD	Mean	SD	Mean	SD			
Bipolar I disorder duration, y	14.7	12.0	12.7	11.6	19.7[a,b]	12.9	F = 16.4	2,654	< .001
AUD duration, y	21.7	12.1	11.9[a]	12.0	12.3[a]	10.8	F = 54.4	2,654	< .001
Lifetime mood episodes	11.7	22.5	9.6	19.4	22.9[a,b]	39.3	F = 10.9	2,573	< .001
Mood episodes per year since bipolar I disorder onset	1.8	6.8	1.3	1.7	1.4	2.3	F = 1.1	2,535	.58
Bipolar I disorder–AUD latency, y	12.6	8.7	…	…	6.6[a]	6.2	F = 516.6	2,653	< .001
AUD treatment latency, y	7.4	11.4	1.6[a]	5.9	1.7[a]	4.9	F = 13.1	2,205	< .001
Bipolar I disorder treatment latency, y	1.7	3.6	1.4	6.4	5.1[a,b]	9.1	F = 9.0	2,256	< .001
Short-Form-12v2[c] score									
Mental disability	43.0	13.2	42.2	12.8	43.4	12.8	F = 0.4	2,653	.70
Social functioning	43.6	13.9	45.8	13.4	45.8	13.0	F = 2.3	2,653	.10
Role emotional function	42.2	14.8	42.4	13.4	43.8	13.7	F = 0.9	2,653	.41
Mental health	43.1	12.5	42.7	11.9	43.2	12.2	F = 0.1	2,653	.91

[a]p < .05 vs. antecedent AUD.
[b]p < .05 vs. same year.
[c]Scores refer to current functioning.

spondents who sought bipolar I treatment ($\chi^2 = 1.0$, df = 2, p = .61). Among those who reported seeking bipolar I treatment, the latency, in years, from bipolar I onset to treatment was significantly greater among Bipolar First (mean = 5.1, SD = 9.1) respondents as compared to Alcohol First (mean = 1.7, SD = 3.6; p < .05) and Same Year (mean = 1.4, SD = 6.4; p < .05) respondents.

Alcohol Use Disorder Severity

There were significant between-group differences in AUD service utilization. Same Year respondents were more likely to report seeking professional help for AUD (42%) than either Alcohol First (30%; $\chi^2 = 4.8$, df = 1, p = .03) or Bipolar First (30%; $\chi^2 = 4.9$, df = 1, p = .03) respondents. Among those who reported seeking AUD treatment, the latency, in years, from AUD onset to AUD treatment was significantly greater among Alcohol First respondents (mean = 7.4, SD = 11.4) as compared to Same Year (mean = 1.6, SD = 5.9; p < .05) and Bipolar First (mean = 1.7, SD = 4.9; p < .05) respondents. The 12-month prevalence of AUD (for the 570 respondents with onset of both bipolar I disorder and AUD prior to the past year) among Alcohol First respondents (24%) was lower than among Same Year (42%; $\chi^2 = 11.1$, df = 1, p < .001) or Bipolar First (39%; $\chi^2 = 13.6$, df = 1, p < .001) respondents. In addition, Alcohol First respondents were less likely to report 12-month prevalence of both bipolar I disorder and AUD (10%) as compared to Bipolar First respondents (18%; $\chi^2 = 6.6$, df = 1, p = .01).

Family History

There were no significant between-group differences in proportion of respondents with parental history of alcoholism ($\chi^2 = 1.2$, df = 2, p = .54) or depression ($\chi^2 = 4.4$, df = 2, p = .11). However, Same Year respondents were significantly more likely to report having a parent with both alcoholism and depression (39%) than Alcohol First (27%; $\chi^2 = 5.9$, df = 1, p = .02) or Bipolar First (28%; $\chi^2 = 4.3$, df = 1, p = .04) respondents.

Exploratory Analyses

Exploratory analyses examining the prevalence of anxiety disorders and personality disorders were conducted (Table 2): Same Year respondents reported a lower lifetime prevalence of anxiety disorders (35%) than Alcohol First (56%) or Bipolar First respondents (48%), although only the difference with Alcohol First was statistically significant ($\chi^2 = 5.3$, df = 1, p = .02). There were no sig-

Table 3. Twelve-Month Prevalence of Bipolar I Disorder and Alcohol Use Disorders (AUD) Among Respondents With Bipolar I Disorder and AUD Prior to the Past 12 Months by Temporal Priority

	Antecedent AUD (N = 264)		Same Year (N = 94)		Antecedent Bipolar I Disorder (N = 212)		Statistics[a]	
Disorder	N	%	N	%	N	%	χ^2	p
12-Month bipolar I disorder[b]	106	40	33	35	92	43	1.9	.39
12-Month AUD[c]	62	24	39	42[d]	83	39[d]	17.6	< .001
12-Month bipolar I disorder and AUD	27	10	15	16	39	18[d]	6.7	.04
12-Month bipolar I disorder or AUD	141	53	57	61	136	64	5.8	.06

[a]df = 2.
[b]12-Month prevalence of manic, mixed, or major depressive episode.
[c]12-Month prevalence of alcohol abuse or dependence.
[d]p < .05 vs. antecedent AUD.

nificant between-group differences in prevalence of personality disorders ($\chi^2 = 4.9$, df = 2, p = .09). Finally, there were no significant between-group differences in the mean scores of the 4 SF-12v2 subscales examined: mental disability (F = 0.4, df = 2,653; p = .70), social functioning (F = 2.3, df = 2,653; p = .10), role emotional health (F = 0.9, df = 2,653; p = .41), or mental health (F = 0.1, df = 2,653; p = .91).

DISCUSSION

The central finding of this study is that temporal priority is associated with between-group differences in comorbid bipolar I disorder–AUD. The results of this study provide support for some but not all of the hypotheses tested. Bipolar First respondents were more likely than Same Year or Alcohol First respondents to report prolonged manic episodes. However, there were no between-group differences in mood episode frequency, chronic rapid cycling, or bipolar I treatment utilization. Alcohol First respondents did not demonstrate increased severity of AUD relative to Same Year or Bipolar First respondents; rather, they showed less persistence of ongoing AUD.

Despite focusing on comorbid bipolar I disorder–AUD, we found low prevalence of rapid cycling across groups. There are several possible explanations for this finding. First, the study describes an epidemiologic sample, with its associated lower severity of pathology as compared to clinical samples. Second, we utilized a conservative definition of rapid cycling that required a mean of at least 4 mood episodes per year since bipolar I onset. The actual prevalence of rapid cycling is likely higher, given that many respondents may have experienced periods of rapid cycling during the course of their illness without averaging 4 episodes per year throughout. We were unable to capture this form of rapid cycling with the available data.

Unexpectedly, Same Year respondents were more likely to receive AUD treatment than either Alcohol First or Bipolar First respondents. Although all respondents included in this study met criteria for lifetime comorbidity of bipolar I disorder and AUD, Same Year respondents are by definition more likely to experience truly concurrent disorders (i.e., 12-month comorbidity). Thus, Berkson's bias[12] may apply even more to Same Year respondents than to Alcohol First or Bipolar First respondents, resulting in a greater likelihood of accessing AUD treatment. The same was not true, however, for bipolar I–related treatment, which was accessed by approximately 50% of respondents in each of the 3 groups. Nonetheless, among respondents who did access treatment, Same Year respondents reported short latency from onset to treatment of both bipolar I disorder and AUD, providing further rationale for invoking Berkson's bias as an explanation.

One possible explanation for the discrepancy is that Same Year respondents showed the lowest prevalence of both lifetime anxiety disorders and personality disorders (although the latter difference did not reach statistical significance), and this may decrease the likelihood of accessing bipolar I treatment more than AUD treatment. Both anxiety disorders[18] and personality disorders[19] have been associated with AUD in bipolar disorder, and the lower prevalence of both of these comorbidities in the Same Year group suggests the possibility that individuals who experience onset of bipolar I disorder and AUD in the same year are qualitatively different than individuals with greater latency between antecedent and consequent comorbid disorders.

There is a possibility that anxiety disorders may be somewhat overshadowed by bipolar I disorder and AUD in the Same Year group, thus accounting for the comparatively low prevalence. However, this effect is likely to be most pronounced during the first year, when both disorders were first experienced. The mean duration of bipolar I disorder in this group exceeds 12 years, and the data indicate that less than 20% of respondents continue to actively (based on 12-month prevalence) manifest both disorders concurrently. Therefore, it could be expected that if these individuals truly experienced lifetime anxiety disorders, there is sufficient time during which the anxiety disorder could have been experienced as such.

The 12-month prevalence of AUD was consistent with previous findings showing that AUD are not persistent

in the context of bipolar I disorder. Strakowski and colleagues[20] found that in the 12 months following a first hospitalization for bipolar disorder, among a subgroup of individuals with comorbid AUD antecedent to or at admission, 43% manifested both AUD and bipolar disorder during the follow-up period, 54% manifested bipolar disorder without AUD, and 0% manifested AUD without bipolar disorder. In another study[21] of participants with comorbid bipolar disorder and substance use disorders (of whom 77% had AUD), symptoms related to bipolar disorder improved only modestly, as compared to a high rate of remission from substance use at 3-year follow-up (61%). Although it is not unexpected that active AUD persisted in the minority of respondents, the lower 12-month prevalence among Alcohol First respondents as compared to Same Year or Bipolar First respondents was unexpected. Recent data from the NESARC[22] suggest that, among all respondents with alcohol dependence prior to the past year (N = 4422), only 25% had 12-month prevalence of alcohol dependence. Although the present study examined AUD (i.e., both alcohol abuse and dependence), these findings suggest that bipolar I disorder may not significantly alter the course of antecedent AUD. However, it must be taken into account that 12-month prevalence and treatment seeking are but 2 ways of estimating AUD severity. Further studies are needed in order to better understand the impact of bipolar disorder on the course of AUD.

Another between-group difference that emerged from the data relates to bipolar I disorder-AUD latency. Among respondents in the Alcohol First group, AUD preceded bipolar I disorder by approximately 12 years. Among respondents in the Bipolar First group, bipolar I disorder preceded AUD by approximately 6 years. The significance of this difference is that the mean AUD treatment latency among Alcohol First respondents (7.4 years) and the mean bipolar I disorder treatment latency among Bipolar First respondents (5.1 years) fall within the bipolar I–AUD latency. In other words, a substantial proportion of respondents who accessed treatment for their temporally primary condition did so prior to the onset of the comorbid condition. Of note, the mean latency of treatment for the temporally secondary condition was 1.7 years among both the Alcohol First and Bipolar First respondents. Therefore, not only is treatment latency diminished for the temporally secondary condition, but this effect is similar in magnitude regardless of which condition is temporally primary.

With respect to family history, we did not expect to replicate Feinman and Dunner's findings for several reasons. First, the sample from that study comprised a heterogeneous sample, less than 25% of whom had bipolar I disorder. Second, the authors themselves acknowledged that family history findings were counterintuitive.[10] Contrary to our predictions, Alcohol First respondents did not report more parental alcoholism than Same Year or Bipolar First respondents, nor did they report significantly less parental depression than Bipolar First respondents. Same Year respondents, however, reported significantly greater prevalence of parental comorbidity than either Alcohol First or Bipolar First respondents. Previous studies have suggested that bipolar disorder–AUD comorbidity is familial,[8,23] and the emergence of both bipolar disorder and AUD in the same year may be a marker of familial comorbidity. However, heritability of mood disorders and AUD has also been repeatedly shown to be independent.[24–26] Therefore, among individuals with lifetime comorbidity of bipolar disorder and AUD, some may suffer from the 2 disorders independently, while for others the comorbidity represents different manifestations of the same illness. Unfortunately, information regarding familial bipolarity was not available, as the AUDADIS-IV includes items examining family history of a major depressive episode and does not distinguish between unipolar and bipolar depression.

The primary limitation of this study, as with any large-scale epidemiologic study, is its reliance on individual structured interviews to determine diagnoses, age at onset thereof, and health service utilization. Specifically, the presence or absence of AUD symptoms was not verified with collateral informants. However, this is not likely to assert a sizeable effect given that collateral information has been shown to correlate highly with self-report among individuals with bipolar disorder and substance use disorders.[27] Another potential limitation of the present study is the focus on major depressive, mixed, and manic episodes. Previous studies of clinical samples have shown that individuals with bipolar disorder are significantly affected by "roughening," subsyndromal episodes, or residual mood symptoms.[28] There may be additional between-group differences in terms of ongoing symptom burden. The same is true for alcohol use, as the present study examined AUD and did not examine subthreshold alcohol-related difficulties. Nonetheless, the SF-12v2 data suggest similar overall psychosocial impairment across groups despite any potential undetected differences in bipolar I disorder– or AUD-related symptoms.

Taken together, the findings of the present study suggest that temporal priority in lifetime comorbid bipolar I disorder–AUD merits consideration. Making a distinction among individuals with comorbid bipolar disorder–AUD based on temporal priority allows for the identification of significant differences in family history, markers of bipolar disorder and AUD severity, treatment utilization and delay thereof, and other comorbidities. One implication of the present study may be the need to screen for bipolar disorder among individuals initially presenting with AUD and to continue to screen for AUD among individuals initially presenting with bipolar disorder, as the onset of the temporally secondary condition—in an epidemiologic

community sample—often occurs after the antecedent condition has been established for several years.

Another implication of the present study is that there may be a subtype of bipolar I disorder–AUD with onset of both illnesses in the same year that is characterized by somewhat lower prevalence of anxiety disorders and personality disorders and somewhat higher prevalence of familial comorbidity. Although others have suggested that it is more important in clinical and genetic research to control for AUD than to examine them directly,[29] careful attention to phenomenology and temporal priority may help delineate specific comorbid phenotypes for genetic studies. Present findings, which require replication, suggest the possibility of a distinct Same Year bipolar I disorder–AUD phenotype. Future studies are needed to examine the impact of temporal priority from a large-scale, prospective, clinical perspective and address genetic contributions to these potentially distinct bipolar I disorder–AUD phenotypes.

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