Original Article

The specific burden of comorbid anxiety disorders and of substance use disorders in bipolar I disorder

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Objectives: Uncertainty exists regarding whether comorbid substance use disorders (SUDs) in bipolar I disorder are more prevalent among persons with versus without comorbid anxiety disorders. Moreover, the independent contribution of these comorbidities to the burden of bipolar disorder (BD) is unclear.

Methods: The 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions was used to identify respondents with lifetime BD (n = 1,411). Illness severity was compared across four groups based on the presence of lifetime anxiety disorders, lifetime SUDs, neither, or both. Variables included lifetime prevalence of mixed mania, prolonged mood episodes, BD-related health service utilization, and forensic history, 12-month prevalence of mania and depression, and current general mental health functioning. Diagnoses were generated using the National Institute on Alcohol Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule, DSM-IV Version. Analyses were computed separately for males and females.

Results: For females only, the lifetime prevalence of SUDs was significantly greater among those with lifetime anxiety disorders [odds ratio (OR) = 1.41, 95% confidence interval (CI) = 1.08–1.86]; this was not found among males (OR = 1.15, 95% CI = 0.79–1.68). In multiple logistic regression analyses among both males and females, anxiety disorders were significantly associated with mixed episodes, prolonged depressive episodes, 12-month prevalence of depression, BD-related health service utilization, and poorer current mental health functioning. SUDs were significantly associated with mixed episodes among females, 12-month prevalence of depression among males, and with forensic history among both males and females.

Conclusions: Whereas comorbid anxiety disorders appear to confer increased liability towards poor mental health functioning and greater BD-related health service utilization, comorbid SUDs are associated with positive forensic history. Early identification and treatment of these comorbid conditions are of paramount importance. Further representative prospective studies are needed.

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The results from three successive large-scale epidemiologic surveys show that substance use disorders (SUDs) are significantly more prevalent among persons with bipolar disorder (BD) than

among unaffected persons or even those with major depressive disorder (1–3), and the same surveys report extremely high prevalence of anxiety disorders among subjects with BD (4–7). Similarly, data from recent clinical studies by the Stanley Foundation Bipolar Treatment Outcome Network (8) and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (5), among others (10–14), confirm that anxiety and SUDs are each highly prevalent in BD. These comorbidities have unequivocal clinical and public health implications. Among patients with BD, SUDs are associated with delayed recovery, hastened relapse, greater inter-episode symptom burden, and increased disability and mortality (15–19). Similarly, comorbid anxiety disorders are associated with earlier age of onset, poorer treatment response, exacerbated global illness severity and functional impairment, and suicidality (6, 20–23).

The two largest clinical studies that report on the association between anxiety disorders and SUDs in BD among both males and females are contradictory (9, 11). A study of the first 500 patients enrolled in STEP-BD found that BD patients with lifetime anxiety disorders had roughly double the prevalence of lifetime alcohol dependence and 50% greater prevalence of lifetime drug dependence compared to BD patients without lifetime anxiety disorders (9). In contrast, Henry et al. (11) report that, among 318 patients with BD, anxiety disorders were not associated with increased current or lifetime history of SUDs. The National Comorbidity Survey found that BD with comorbid panic attacks is associated with increased prevalence of drug use disorders but not alcohol use disorders (AUDs) (6). To date, it is unclear whether or not all anxiety disorders are associated with increased prevalence of both alcohol and drug use disorders among patients with BD.

Another question that arises is whether individuals with BD and anxiety disorders differ significantly from those with BD and SUDs in terms of demographic, clinical, and health service-related characteristics. Further, how do patients with BD and comorbid anxiety disorders or SUDs compare to BD patients with both anxiety disorder and SUD comorbidity? The literature that addresses these questions is relatively sparse, and is based almost exclusively on clinical samples (10, 24, 25). An epidemiologic perspective to address these questions is needed in order to overcome some of the potential biases inherent in clinical samples (26).

Finally, there is an emerging literature indicating that individuals with bipolar disorders are over-represented in the criminal justice system, and that this is particularly true of patients with comorbid SUDs (27, 28). Therefore, when comparing the impact of various comorbidities on the course, outcome, and burden of BD, it is important to consider as barometers of severity both health-service utilization and the prevalence of forensic history, including arrest and incarceration.

This study examines the association between lifetime anxiety disorders and lifetime SUDs, and the specific association of each of these comorbidities with the burden of bipolar illness, in an epidemiologic sample of subjects with BD. The following hypotheses were examined: (i) the prevalence of SUDs among individuals with any lifetime anxiety disorder is not significantly greater than among those without lifetime anxiety disorders; (ii) the prevalence of SUDs is significantly higher among individuals with panic disorder compared to those without panic disorder; (iii) BD subjects with both anxiety and SUD comorbidity manifest more severe bipolar illness (as reflected by a history of mixed mania, greater 12-month prevalence of mood episodes, chronic mood episodes, general mental health functioning) compared to BD subjects with only one of these comorbidities; (iv) comorbid anxiety disorders are associated with increased health service utilization; and comorbid SUDs are associated with increased prevalence of forensic history.

Methods

Subjects

Subjects were identified from among the respondents of the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Respondents with lifetime independent bipolar I disorder (n = 1,411) were included in the present study, and were divided into four groups for the purpose of analyses: respondents with no substance or anxiety comorbidity (BD-only; n = 311, 22%), respondents with comorbid anxiety disorders only (BD-ANX; n = 250, 18%), respondents with comorbid SUDs only (BD-SUD; n = 433, 31%), and respondents with both comorbid anxiety disorders and comorbid SUDs (BD-ANX-SUD; n = 420, 30%). The NESARC is a representative sample of the USA conducted by the National Institute on Alcoholism and Alcohol Abuse (NIAAA). A detailed description of the NESARC has been described in detail elsewhere (3). Briefly, 43,093 non-institutionalized civilian respondents, aged 18 years and older, completed face-to-face computer-assisted personal interviews. The overall survey response rate was 81%.

Assessment

Approximately 1,800 lay interviewers with an average of five years of 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) was used to generate the diagnoses presented in this report. The AUDADIS-IV diagnoses of personality disorders, substance use disorders (7), and mood and anxiety disorders (3, 29), have demonstrated reliability and validity. Reliability of the BD diagnosis ($\kappa = 0.59$) is fair (30), while the reliability is excellent for alcohol diagnoses ($\kappa \geq 0.74$) and drug diagnoses ($\kappa \geq 0.79$) (3). The anxiety disorders included in the present study are social phobia, panic disorder (with and without agoraphobia), and generalized anxiety disorder, and these have fair to good reliability ($\kappa = 0.42–0.52$) (30). Reliability of the personality disorder diagnoses also ranges from fair to good, from $\kappa = 0.4$ for histrionic personality disorder to $\kappa = 0.67$ for antisocial personality disorder (29). Age at onset of BD (i.e., age at first manic/mixed episode), lifetime number of mood episodes, family history, treatment history, forensic history, and demographic variables were all determined from the AUDADIS-IV. Forensic history was considered positive if the respondent endorsed having been arrested, held at a police station, or jailed in the context of a manic or mixed episode. Information regarding forensic history incurred other than during a manic or mixed episode was not available.

The NESARC also includes among its measures the SF-12v2, 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 (31). The present study focused on four SF-12v2 health survey scores that reflect general social and emotional functioning: 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 score of 50 and an SD 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. BD was classified as independent of substance use if: (i) the respondent abstained from alcohol and drug use in the 12 months preceding the assessment; (ii) the episode(s) did not occur in the context of alcohol or drug intoxication or withdrawal; (iii) the episode(s) occurred before alcohol or drug intoxication or withdrawal; or, (iv) the episode(s) began after alcohol or drug intoxication or withdrawal, but persisted for more than one 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 BD group analyses.

Statistical analyses

Odds ratios (OR) with 95% confidence intervals (CI) were computed to detect differences in the prevalence of SUDs among subjects with and without anxiety disorders.

Multiple 2×4 contingency tables were created to detect differences on categorical measures between the four groups examined (i.e., BD-only, BD-ANX, BD-SUD, BD-ANX-SUD). Chi-squared analysis was used to detect for statistical significance. Pair-wise *post hoc* comparisons (2×2 contingency tables) were computed only where the omnibus comparison (2×4 contingency table) was statistically significant. One-way analysis of variance (ANOVA) was used to compare differences between these groups on dimensional measures. *Post hoc* Tukey pairwise comparisons were computed if the ANOVA was statistically significant. Statistical significance was corrected for multiple comparisons (0.05/12) and *post hoc* comparisons were only computed for analyses with p < 0.004.

Multiple logistic regression analyses were conducted for the BD severity-related variables and health service utilization-related variables for which omnibus comparisons were significant, and for forensic history. These analyses were conducted in order to examine the unique contribution of the independent categorical variables, lifetime anxiety disorders and lifetime SUDs, to the variance in the dependent variables (i.e., BD severity, BD-related health service utilization, forensic history) among subjects with BD. Demographic and illness course variables for which there were significant between-group differences in univariate or cross-tabulation analyses were included as variables in multiple logistic regression analyses.

Analyses were conducted separately for males and females owing to the known gender differences in comorbidity in BD (32, 33).

Statistical analyses were performed using SPSS, version 13 (SPSS Inc., Chicago, IL, USA). 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 (3, 7).

Results

Lifetime prevalence of substance use disorders based on presence or absence of anxiety disorders

The first question addressed in this study is whether lifetime SUDs are in fact more prevalent amongst BD subjects with, compared to without, lifetime anxiety disorders. The odds ratios with 95% confidence intervals were determined for SUDs among subjects with any anxiety disorder, and separately for subjects with social phobia, panic disorder, generalized anxiety disorder, compared to those without these disorders (Table 1). The results for males and females are presented separately.

Among males, subjects with panic disorder had significantly higher prevalence of SUDs (OR = 2.16, 95% CI = 1.26–3.71) compared to subjects without panic disorder. Males with social phobia or generalized anxiety disorder did not have a higher prevalence of SUDs compared to those without these disorders. Among females, there was a significantly higher prevalence of SUDs among subjects with any anxiety disorder (OR = 1.41,

95% CI = 1.08–1.86), social phobia (OR = 1.49, 95% CI = 1.08–2.07), generalized anxiety disorder (OR = 1.13, 95% CI = 1.04–1.92), and panic disorder (OR = 1.60, 95% CI = 1.19–2.15) compared to subjects without these disorders.

Comparison of respondents with bipolar I disorder based on presence of anxiety disorders, substance use disorders, or both

Subjects were divided into the four groups described above and compared on the basis of BD severity, BD-related health service utilization, and BD-related forensic history. As with the previous analyses, these analyses were repeated separately for males (Table 2) and females (Table 3).

Bipolar disorder severity. This study included the following proxies for BD severity: mixed mania, 12-month prevalence of depression and mania, lifetime prevalence of prolonged mood episodes, and general mental health functioning.

The comparison of the four groups in terms of illness severity is reported in Tables 2 and 3 for males and females, respectively. The overall finding is that, in general, the illness severity of BD-ANX subjects was not significantly different from that of BD-ANX-SUD subjects, and that the illness severity of subjects in each of these groups was significantly greater than that of subjects in both the BD-only and BD-SUD groups. The illness severity of BD-only subjects was not significantly different from that of BD-SUD subjects. This was true of mixed mania, 12-month prevalence of depression, and lifetime prevalence of chronic depressive episodes. Although the same general pattern was observed for 12-month prevalence of mania and lifetime prevalence of chronic mania, the between-group differences were not statistically significant.

The general finding in the multiple logistic regression analyses, among both males and females, was that anxiety disorders were consistently significantly associated with markers of BD severity, whereas this was less consistently true for SUDs. Multiple logistic regression analyses for males included as covariates age, duration of BD, and race. Anxiety disorders independently contributed significantly to the presence/absence of mixed mania ($\chi^2 = 36.7$, df = 1, p < 0.001), but this was not true of SUDs ($\chi^2 = 2.1$, df = 1, p = 0.14). Similarly, anxiety disorders independently contributed significantly to the presence/absence of a lifetime prolonged (≥ 12 months) depressive episode ($\chi^2 = 23.8$, df = 1, p < 0.001), but this was not true of SUDs ($\chi^2 = 0.0$, df = 1, p = 0.91).

Table 1. Lifetime odds ratios of lifetime substance use disorders[a] among bipolar I disorder subjects with versus without lifetime anxiety disorders

	Present, n (%)	Absent, n (%)	OR (CI)[b]
Any anxiety			
Males	188/247 (76)	244/332 (74)	1.15 (0.79–1.68)
Females	232/423 (55)	189/409 (46)	1.41 (1.08–1.86)[c]
Social phobia			
Males	92/126 (73)	340/453 (75)	0.90 (0.56–1.41)
Females	113/194 (58)	308/638 (48)	1.49 (1.08–2.07)[c]
Panic disorder			
Males	100/118 (85)	332/461 (72)	2.16 (1.26–3.71)[d]
Females	154/263 (59)	267/569 (47)	1.60 (1.19–2.15)[d]
Generalized anxiety disorder			
Males	84/110 (76)	348/469 (74)	1.12 (0.69–1.83)
Females	134/236 (57)	287/596 (48)	1.41 (1.04–1.92)[c]

[a]Any alcohol or drug use disorder.
[b]OR (CI) = odds ratio (95% confidence interval); the ORs represent the odds of having a substance use disorder among bipolar disorder (BD) individuals with anxiety disorders relative to the odds of having a substance use disorder among BD individuals who do not have anxiety disorders.
[c]p < 0.05.
[d]p < 0.01.

Table 2. Clinical and demographic characteristics of 579 male bipolar I disorder subjects with or without lifetime anxiety and substance use disorder (SUD) comorbidity

	BD-only[a] (n = 88; 15%)		BD-ANX[b] (n = 59; 10%)		BD-SUD[c] (n = 244; 42%)		BD-ANX-SUD[d] (n = 188; 33%)		Statistic	Post hoc test[f]
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)		
Personal income[e]	20.0	17.4	27.4	26.1	25.9	27.6	25.1	26.4	$F = 1.4$, df = 3,575, $p = 0.25$	
Age	35.3	16.7	43.4	16.6	36.3	15.2	40.5	13.8	$F = 6.3$, df = 3,575, $p < 0.001$	a = c < b = d
Age of mania onset	20.7	11.6	25.6	14.5	22.2	11.6	22.8	10.6	$F = 6.3$, df = 3,546, $p = 0.11$	
Bipolar duration (years)	14.4	14.7	18.0	14.7	13.7	12.3	17.6	12.7	$F = 3.8$, df = 3,546, $p = 0.01$	
	n	%	n	%	n	%	n	%		
Caucasian	63	72	51	86	197	81	158	84	$\chi^2 = 7.3$, df = 3, $p = 0.06$	
Married	33	38	24	41	104	43	81	43	$\chi^2 = 0.9$, df = 3, $p = 0.83$	
Mixed mania only	21	25	27	47	67	29	101	54	$\chi^2 = 38.0$, df = 3, $p < 0.001$	a = c < b = d
12-month mania prevalence	45	51	32	54	110	45	90	48	$\chi^2 = 2.1$, df = 3, $p = 0.55$	
Mania > 6 months	26	30	22	37	80	33	65	35	$\chi^2 = 1.1$, df = 3, $p = 0.77$	
12-month depression prevalence	23	26	28	48	50	21	63	34	$\chi^2 = 20.7$, df = 3, $p < 0.001$	a = c < b = d
Depression > 12 months	16	14	22	37	42	17	69	37	$\chi^2 = 29.9$, df = 3, $p < 0.001$	a = c < b = d
Personality disorder	44	50	40	68	154	63	153	81	$\chi^2 = 31.0$, df = 3, $p < 0.001$	a < b = c < d
Emergency visit for mania	4	5	5	9	11	5	33	18	$\chi^2 = 24.6$, df = 3, $p < 0.001$	a = b = c < d
Admitted for mania	4	5	6	10	25	10	30	16	$\chi^2 = 8.5$, df = 3, $p = 0.04$	
Emergency visit for depression	4	5	8	14	21	9	38	20	$\chi^2 = 19.0$, df = 3, $p < 0.001$	a < b = d, c < d
Admitted for depression	3	3	8	14	30	12	50	27	$\chi^2 = 29.2$, df = 3, $p < 0.001$	a < b = c < d
Any bipolar utilization	17	19	35	59	80	33	103	55	$\chi^2 = 47.0$, df = 3, $p < 0.001$	a < c < b = d
Arrested or jailed	9	10	9	15	65	27	45	24	$\chi^2 = 11.9$, df = 3, $p = 0.008$	a < c < b = d

BD = bipolar disorder.
[a]BD-only = respondents with no substance or anxiety comorbidity.
[b]BD-ANX = respondents with comorbid anxiety disorders only.
[c]BD-SUD = respondents with comorbid SUDs only.
[d]BD-ANX-SUD = respondents with both comorbid anxiety disorders and comorbid SUDs.
[e]Expressed in thousands of US dollars.
[f]Unless otherwise noted, pair-wise differences were not statistically significant (p < 0.004 after Bonferroni correction for multiple comparisons).

Table 3. Clinical and demographic characteristics of 832 female bipolar I disorder subjects with or without lifetime anxiety and substance use disorder (SUD) comorbidity

	BD-only[a] (n = 220; 26%)		BD-ANX[b] (n = 191; 23%)		BD-SUD[c] (n = 189; 23%)		BD-ANX-SUD[d] (n = 232; 28%)		Statistic	Post hoc test[f]
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)		
Personal income[e]	14.8	16.5	15.1	18.6	17.3	17.4	15.4	15.9	$F = 0.8$, df $= 3,828$, p $= 0.48$	
Age	40.0	16.2	43.9	15.7	35.9	13.4	38.3	11.8	$F = 10.5$, df $= 3,828$, p < 0.001	b > a,c,d; a > c
Age of mania onset	25.0	13.1	25.1	14.0	21.5	10.3	20.6	9.6	$F = 8.0$, df $= 3,791$, p < 0.001	a = b > c = d
Bipolar duration	14.3	12.3	18.0	15.4	13.8	12.0	17.6	11.9	$F = 5.6$, df $= 3,791$, p $= 0.001$	a = c < b = d
	n	%	n	%	n	%	n	%		
Caucasian	146	66	136	71	139	74	190	82	$\chi^2 = 14.6$, df $= 3$, p $= 0.002$	a = b = c < d
Married	103	47	76	40	79	42	91	39	$\chi^2 = 3.2$, df $= 3$, p $= 0.36$	
Mixed mania only	79	37	92	49	85	46	132	58	$\chi^2 = 20.1$, df $= 3$, p < 0.001	a < b, a = c < d
12-month mania prevalence	109	50	113	59	91	48	134	58	$\chi^2 = 7.7$, df $= 3$, p $= 0.05$	
Mania > 6 months	59	27	63	33	55	29	80	35	$\chi^2 = 1.1$, df $= 3$, p $= 0.77$	
12-month depression prevalence	70	32	99	52	69	37	136	59	$\chi^2 = 42.0$, df $= 3$, p < 0.001	a = c < b = d
Depression > 12 months	58	26	77	43	45	24	115	50	$\chi^2 = 41.3$, df $= 3$, p < 0.001	a = c < b = d
Personality disorder	99	45	133	70	107	57	187	81	$\chi^2 = 68.5$, df $= 3$, p < 0.001	a < c < b < d
Emergency visit for mania	13	6	36	19	8	4	39	17	$\chi^2 = 33.0$, df $= 3$, p < 0.001	a = c < b = d
Admitted for mania	18	8	36	19	17	9	43	19	$\chi^2 = 18.1$, df $= 3$, p < 0.001	a = c < b = d
Emergency visit for depression	27	12	59	31	28	15	64	28	$\chi^2 = 31.3$, df $= 3$, p < 0.001	a = c < b = d
Admitted for depression	30	14	53	28	37	20	74	32	$\chi^2 = 24.7$, df $= 3$, p < 0.001	a = c < b = d
Any bipolar utilization	107	49	135	71	107	56	176	76	$\chi^2 = 44.1$, df $= 3$, p < 0.001	a = c < b = d
Arrested or jailed	4	2	4	2	20	11	25	11	$\chi^2 = 26.7$, df $= 3$, p < 0.001	a = b < c = d

BD = bipolar disorder.
[a]BD-only = respondents with no substance or anxiety comorbidity.
[b]BD-ANX = respondents with comorbid anxiety disorders only.
[c]BD-SUD = respondents with comorbid SUDs only.
[d]BD-ANX-SUD = respondents with both comorbid anxiety disorders and comorbid SUDs.
[e]Expressed in thousands of US dollars.
[f]Unless otherwise noted, pair-wise differences were not statistically significant (p < 0.004 after Bonferroni correction for multiple comparisons).

In contrast, both anxiety disorders ($\chi^2 = 18.5$, df = 1, p < 0.001) and SUDs ($\chi^2 = 4.0$, df = 1, p = 0.04) independently contributed significantly to the 12-month prevalence of depression.

Multiple logistic regression analyses for females included as covariates age, age of mania onset, duration of bipolar illness, and race. Anxiety disorders independently contributed significantly to the 12-month prevalence of major depression ($\chi^2 = 23.4$, df = 1, p < 0.001), but this was not true of SUDs ($\chi^2 = 0.3$, df = 1, p = 0.60). Similarly, anxiety disorders independently contributed significantly to the presence/absence of lifetime history of a depressive episode of > 12 months in duration ($\chi^2 = 20.4$, df = 1, p < 0.001), but this was not true of SUDs ($\chi^2 = 1.1$, df = 1, p = 0.30). In contrast, both anxiety disorders ($\chi^2 = 6.9$, df = 1, p = 0.009) and SUDs ($\chi^2 = 5.1$, df = 1, p = 0.02) independently contributed significantly to the presence/absence of mixed mania.

Another measure of illness severity is general mental health functioning (Table 4). The specific components included SF-12v2 scales for mental disability, social functioning, role emotional functioning, and mental health. The pattern that emerged indicates that the mean general mental health of BD-ANX subjects was not significantly different from that of BD-ANX-SUD subjects, and the mean general mental health of each of these groups was significantly lower than that of both BD-only and BD-SUD subjects. The mean general mental health of BD-only subjects was not significantly different from that of BD-SUD subjects. This pattern was observed across each of the four scales examined among both males and females.

Linear regression analyses, including the same covariates as the previous logistic regression analyses, were conducted to examine the unique contribution of lifetime anxiety disorders and SUDs to the variance in these four scales. Among both males and females, respectively, anxiety disorders independently contributed significantly to lower scores on the mental disability ($t = -5.5$, df = 1, 542, p < 0.001; $t = -8.3$, df = 1,789, p < 0.001), social functioning ($t = -5.2$, df = 1,542, p < 0.001; $t = -6.9$, df = 1,789, p < 0.001), role emotional ($t = -4.1$, df = 1,542, p < 0.001; $t = -7.0$, df = 1,789, p < 0.001), and mental health ($t = -5.7$, df = 1,542, p < 0.001; $t = -7.4$, df = 1,542, p < 0.001) scales. In contrast, SUDs among males were significant predictors only of lower scores on the mental health scale ($t = -2.2$, df = 1,542, p = 0.03). There was also a statistical trend toward greater mental disability among males with SUD ($t = -1.8$, df = 1,542, p = 0.07). Among females, SUDs were significant predictors only of

Table 4. General mental health functioning among bipolar I disorder subjects with or without lifetime anxiety and substance use disorder (SUD) comorbidity

	BD-only[a]		BD-ANX[b]		BD-SUD[c]		BD-ANX-SUD[d]		Statistic	Post hoc
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)		
Males	(n = 88)		(n = 59)		(n = 244)		(n = 188)			
Mental component summary	49.0	11.5	43.9	11.7	47.5	11.3	41.9	12.8	F = 11.1, df = 3,573, p < 0.001	a = c > b = d
Social functioning	49.4	12.5	44.1	14.3	49.1	11.0	42.7	14.3	F = 11.1, df = 3,573, p < 0.001	a = c > b = d
Role emotional	47.3	13.1	42.4	13.3	46.8	12.7	41.6	14.7	F = 7.0, df = 3,573, p < 0.001	a = c > b = d
Mental health	49.8	10.9	43.9	10.5	47.3	11.3	45.5	11.9	F = 12.5, df = 3,573, p < 0.001	a = c > b = d
Females	(n = 220)		(n = 191)		(n = 189)		(n = 232)			
Mental component summary	45.2	11.8	37.4	12.5	44.3	11.8	37.0	13.8	F = 25.7, df = 3,828, p < 0.001	a = c > b = d
Social functioning	46.0	12.6	39.5	14.9	46.3	12.8	39.1	14.4	F = 17.4, df = 3,828, p < 0.001	a = c > b = d
Role emotional	45.4	12.3	38.4	14.5	44.7	12.2	37.2	14.3	F = 21.2, df = 3,828, p < 0.001	a = c > b = d
Mental health	44.5	12.3	37.2	11.8	43.8	11.2	38.0	12.6	F = 20.7, df = 3,828, p < 0.001	a = c > b = d

General mental health functioning was determined by examining the four Short-Form-12v2 scores that reflect general mental health functioning.
BD = bipolar disorder.
[a]BD-only = respondents with no substance or anxiety comorbidity.
[b]BD-ANX = respondents with comorbid anxiety disorders only.
[c]BD-SUD = respondents with comorbid SUDs only.
[d]BD-ANX-SUD = respondents with both comorbid anxiety disorders and comorbid SUDs.

lower role emotional scores ($t = -2.0$, df = 1,789, p = 0.04).

Each of the regression analyses was repeated with an SUD × anxiety interaction term, and no significant interactions between anxiety disorders and SUDs were found (results not shown).

Bipolar disorder-related health service utilization. Univariate analyses for males (Table 2) demonstrated that the prevalence of BD-related health service utilization was consistently lowest among BD-only subjects and highest among BD-ANX-SUD subjects. BD-ANX subjects had significantly greater prevalence of any BD service utilization compared to BD-SUD subjects, but were not significantly different with respect to any specific types of BD service utilization. Compared to BD-ANX-SUD subjects, BD-SUD subjects were significantly less likely to report any BD service utilization, and this was true for specific types of BD service utilization as well. BD-ANX subjects were not significantly different from BD-ANX-SUD subjects in terms of overall BD service utilization.

Univariate analyses for females (Table 3) demonstrated that the prevalence of BD-related health service utilization among BD-ANX subjects was not significantly different from that of BD-ANX-SUD subjects. The prevalence of BD-related health service utilization among both BD-ANX and BD-ANX-SUD subjects was significantly higher than among both BD-only and BD-SUD subjects, and the BD-only and BD-SUD groups did not differ significantly.

In multiple logistic regression analyses among males, anxiety disorders independently contributed significantly to the presence/absence of overall BD-related health service utilization ($\chi^2 = 35.3$, df = 1, p < 0.001), but this was not true of SUDs ($\chi^2 = 1.4$, df = 1, p = 0.24). Anxiety disorders also independently contributed significantly to the presence/absence of emergency department visits for mania ($\chi^2 = 16.1$, df = 1, p < 0.001), whereas this was not true for SUDs ($\chi^2 = 1.1$, df = 1, p = 0.29). In contrast, both anxiety disorders ($\chi^2 = 15.2$, df = 1, p < 0.001) and SUDs ($\chi^2 = 4.2$, df = 1, p = 0.04) independently contributed significantly to the presence/absence of emergency department visits for depression. Both anxiety disorders ($\chi^2 = 18.8$, df = 1, p < 0.001) and SUDs ($\chi^2 = 13.4$, df = 1, p < 0.001) also independently contributed significantly to the presence/absence of hospitalizations for depression.

Multiple logistic repression analyses among females revealed that anxiety disorders independently contributed significantly to the presence/

absence of utilization of any BD-related health service ($\chi^2 = 21.2$, df = 1, p < 0.001), but this was not true of SUDs ($\chi^2 = 1.6$, df = 1, p = 0.20). The same pattern was found for specific types of BD-related service utilization. Anxiety disorders independently contributed significantly to the presence/absence of hospitalizations for mania ($\chi^2 = 12.5$, df = 1, p < 0.001) and for depression ($\chi^2 = 8.3$, df = 1, p = 0.004). However, SUDs did not independently contribute significantly to the presence/absence of hospitalizations for mania ($\chi^2 = 0.0$, df = 1, p = 0.84) or for depression ($\chi^2 = 3.2$, df = 1, p = 0.07). Similarly, anxiety disorders independently contributed significantly to the presence/absence of emergency department visits for mania ($\chi^2 = 26.2$, df = 1, p < 0.001), but this was not true of SUDs ($\chi^2 = 0.4$, df = 1, p = 0.51). Finally, anxiety disorders independently contributed significantly to the presence/absence of emergency department visits for depression ($\chi^2 = 14.4$, df = 1, p < 0.001), but this was not true of SUDs ($\chi^2 = 0.2$, df = 1, p = 0.66).

Again, each of the regression analyses was repeated with an SUD × anxiety interaction term, and no significant interactions between anxiety disorders and SUDs were found (results not shown).

Bipolar disorder-related forensic history. Among females, the presence of a positive forensic history among BD-SUD subjects was not significantly different from BD-ANX-SUD subjects (Table 3). The presence of positive forensic history in these groups was significantly greater than amongst BD-ANX and BD-only subjects, who were not significantly different from each other. The same general pattern was observed among males (Table 2); however, the between-group difference was reduced to a statistical trend after correction for multiple comparisons (p < 0.008).

Multiple logistic regression analyses among females demonstrated that SUDs independently contributed significantly to the presence of forensic history ($\chi^2 = 26.7$, df = 1, p < 0.001), but this was not true of anxiety disorders ($\chi^2 = 0.0$, df = 1, p = 0.99). Exploratory analyses were computed for males due to the statistical trend that was observed (p < 0.008; Table 2). Multiple logistic regression analysis among males indicated that SUDs independently contributed significantly to the presence of forensic history ($\chi^2 = 11.2$, df = 1, p = 0.001), but this was not true of anxiety disorders ($\chi^2 = 0.2$, df = 1, p = 0.67). Due to the known association between antisocial personality disorder (ASPD) and forensic history (34), analyses were repeated including ASPD as a variable

rather than any personality disorder. ASPD independently contributed significantly to the presence of positive forensic history among males ($\chi^2 = 18.2$, df $= 1$, p < 0.001), but not among females ($\chi^2 = 1.1$, df $= 1$, p $= 0.30$). After controlling for ASPD, SUDs independently contributed significantly to the presence of forensic history among both males ($\chi^2 = 5.3$, df $= 1$, p $= 0.02$) and females ($\chi^2 = 24.0$, df $= 1$, p < 0.001).

As with the previous analyses, no significant interactions between anxiety disorders and SUDs were found (results not shown).

Discussion

The results of this study demonstrate that the relationship between anxiety disorders, SUDs, and BD varies significantly based on gender and the specific type of anxiety disorder. To our knowledge, this epidemiologic study is the first to incorporate each of these dimensions with sufficient statistical power. Comorbid anxiety disorders among females with bipolar disorder were associated with significantly but modestly increased prevalence of SUDs. Among males, in contrast, only panic disorder was associated with significantly increased prevalence of SUDs.

In the general population, the presence of any anxiety disorder is significantly associated with SUDs, a finding which has been replicated in the Epidemiologic Catchment Area (1), National Comorbidity Survey (NCS) (2, 35), and NESARC (3) surveys. However, the present study examines only subjects with BD, and there are few data with which to compare present findings. Goodwin and Hoven (6) previously reported that comorbid panic was associated with a significantly increased prevalence of substance dependence among subjects with BD in the NCS. Frye et al. (36) reported that social phobia and panic disorder were significantly associated with alcoholism among females but not among males. However, in that study, the statistical comparisons relating to specific anxiety disorders among males were underpowered (i.e., < 10 subjects in multiple cells). The study of inpatient veterans with BD by Bauer et al. (10) was composed predominantly of males and did not report findings separately for males and females. The significant association between anxiety disorders and SUDs among females with BD in the present study converges with findings reported by Frye et al. (36). Similarly, the finding that panic disorder is associated with increased prevalence of SUDs among both males and females is consistent with results from the NCS, which examined males and females together (6). In contrast, the finding that only panic disorder is associated

with increased prevalence of SUDs among males with BD is unexpected and requires replication.

This study also examined the unique contribution of anxiety disorders and SUDs to the variance in several proxies for BD severity. Among both males and females, lifetime anxiety disorders were uniquely and significantly associated with the 12-month prevalence of depression, and with lifetime prevalence of mixed episodes and prolonged depressive episodes. SUDs among males were significantly associated only with 12-month prevalence of depression, and SUDs among females were significantly associated only with the lifetime prevalence of mixed episodes. With respect to overall mental health functioning, subjects with comorbid SUDs alone were not significantly different from those with BD alone, and subjects with comorbid anxiety disorders were not significantly different from those with both comorbid anxiety and comorbid SUDs. Therefore, current mental health functioning appears to be worse for BD subjects with lifetime anxiety disorders, whereas no such association is apparent for lifetime SUDs.

The more pronounced association of anxiety disorders, compared to SUDs, with certain markers of BD severity converges with results of previous studies. In a recent study by Bauer et al. (10) utilizing a predominantly male sample of inpatient veterans with BD, subjects with comorbid anxiety alone had a greater number of past-year depressive episodes and lower self-reported mental function. Similarly, Perlis et al. (37) reported results from the STEP-BD study showing that current anxiety disorders, but not current SUDs, conferred an increased risk of depressive recurrence. Perlis et al. (37) also reported that current SUDs, but not anxiety disorders, conferred an increased risk of manic/hypomanic/mixed recurrence. However, *lifetime* anxiety disorders or SUDs were not significantly associated with earlier mood episode recurrence (37). Other data from the STEP-BD group, however, have indicated that lifetime anxiety disorders are also significantly associated with multiple measures of BD severity (9). Of note, the same study reported no significant interaction of anxiety with substance use in predicting BD severity and overall impairment (9). The regression analyses in the present study were repeated with an interaction term, and the results corroborated the lack of a significant interaction between anxiety disorders and SUDs (results not shown).

Previously reported data from the NESARC suggest that SUDs may be less persistent and/or recurrent than anxiety disorders among subjects with BD (7). For example, there was much greater

lifetime versus 12-month prevalence of drug use disorders (37.5% versus 12.9%) and alcohol use disorders (58.0% versus 23.6%), whereas the lifetime and 12-month prevalence of anxiety disorders was similar (56.3% versus 48.5%) (7). The greater persistence and/or recurrence of anxiety disorders versus SUDs may explain in part the strength of the association between anxiety disorders and BD severity found in the present study.

The findings regarding BD-related health service utilization mirrored those of BD severity. Overall BD-related health service utilization, emergency department visits, and hospitalizations were significantly greater among subjects with lifetime anxiety disorders, although this was not generally true of SUDs (with the exception of depression-related service use among males). In addition to the issue of persistence/recurrence described above, there are several possible explanations that may account for the surprisingly minimal association between comorbid SUDs and BD-related health service utilization in this study. First, persons with BD and SUDs may manifest symptoms in such a way as to come to legal rather than clinical attention (27, 28). In support of this explanation, SUDs remained significantly associated with positive forensic history after controlling for various potential confounds, most notably antisocial personality disorder. A second explanation, for which there is support in the literature, is that BD often goes unrecognized among persons with comorbid SUDs, such that they seek or are referred to solely substance-related treatment (38, 39). There is also evidence that various factors, such as lack of health insurance, act as barriers to use of mental health services but not specialty SUD services (40). Finally, SUDs are associated with increased physical impairment and burden of medical illness, which is known to be a major public health problem associated with BD (41). Therefore the contribution of SUDs to illness burden in BD may stem from legal and physical sequelae, whereas the burden of anxiety disorders is more likely to stem from psychiatric sequelae.

This study extends previous findings by including personality disorders in the analyses, which is important because personality disorders have been shown both to be more prevalent among subjects with SUDs (42), and to be associated with the severity of mood symptoms among BD patients in remission (43). The prevalence of personality disorders differed significantly between groups, and personality disorders contributed significantly to the variance in several of the multiple logistic regression analyses in this study, as was the case for ASPD in the multiple logistic regression analyses

examining forensic history. The fact that the analyses of this study took into account the potentially confounding effect of personality disorders underscores the specificity of the contribution of SUDs and anxiety disorders to the outcome variables examined herein.

Within the present sample of 1,411 subjects with BD, 30% had both lifetime anxiety disorders and lifetime SUDs. Although there are no previous epidemiologic estimates with which to compare this finding, two previous studies with large clinically derived samples have reported that 37% of BD subjects had both lifetime anxiety disorders and lifetime SUDs (9, 10). It appears that approximately one-third of subjects with BD, whether identified in clinical or epidemiologic studies, have lifetime comorbidity of both anxiety disorders and SUDs.

The results of the present study are tempered by several inherent methodological limitations. The primary limitation of this study, as with any large-scale epidemiologic study, is its reliance on lay interviewer-administered structured interviews to determine diagnoses. In addition, it was not possible to corroborate self-reported health service use with clinical or administrative records. Therefore, reliability of self-reported health service use could not be determined, and the degree to which this is affected by recall bias is unknown. Data regarding lifetime suicide attempts were not available. Given that SUDs have been consistently associated with suicide attempts among persons with BD (19, 44), this may contribute to an underestimate of the illness burden conferred by SUDs. Another potential limitation is that the extent and sequelae of substance use was not verified with collateral informants, and this limits the accuracy of the data. The determination of forensic history was limited to events that occurred during a manic or mixed episode; data regarding forensic history occurring during a depressive episode, during episodes of anxiety exacerbation, or during euthymic periods were not available. There may be unrecognized between-group differences in forensic history not incurred in the context of mania and therefore not captured in the analyses. One of the strengths of this study is the examination of multiple specific anxiety disorders. However, the 2001–2002 NESARC, from which this study is derived, does not yield diagnoses for obsessive–compulsive disorder or post-traumatic stress disorder and this limited the detail in which this study could examine the association between SUDs and severe anxiety disorders in BD. Finally, most previous studies which address the association between anxiety disorders and SUDs in BD describe clinically ascertained samples (8–11, 13, 36, 37);

therefore, the findings of the present study cannot be directly compared to those of previous studies.

Despite these limitations, the present study confirms and extends considerably previous findings. The results of this study confirm the need for especially heightened clinical vigilance for SUDs among females with BD who have anxiety disorders and among males and females with BD who have panic disorder specifically. Of particular importance among the findings of this study are the outcomes for forensic history and the markers of BD illness burden. Whereas comorbid anxiety disorders in BD are more broadly associated with elevated BD severity and BD-related health service use, comorbid SUDs are associated with higher rates of positive forensic history. Early identification and treatment of persons with comorbid BD and SUDs, particularly those who do not suffer from the anxiety disorders that often result in BD-related service use, may attenuate the risks and sequelae of BD-related forensic activity. This is important in light of recent evidence demonstrating efficacy of pharmacotherapy (45) and of psychosocial interventions (46) in this population.

Future studies are needed to examine the impact of temporal priority of onset of these comorbid disorders on the findings described in this and previous related studies. Studies examining specific interventions for anxiety in BD are urgently needed. Cognitive-behavioral therapy (CBT), for example, has been shown to be highly effective in anxiety disorders and in BD (47), but no studies to our knowledge have examined CBT for anxiety in BD specifically.

Ultimately, representative, prospective, longitudinal studies will be required in order to mitigate the limitations of cross-sectional epidemiologic studies such as this one. Nonetheless, these findings contribute to a growing body of literature that informs our understanding of the specific contributions of anxiety disorders and SUDs to illness severity, health service utilization, and forensic involvement among persons suffering from BD.

Acknowledgements

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