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Course of comorbid anxiety disorders among adults with bipolar disorder in the U.S. population

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ABSTRACT

Objective: To examine the prevalence and correlates of comorbid anxiety disorders among individuals with bipolar disorders (BP) and their association with prospectively ascertained comorbidities, treatment, and psychosocial functioning.
Method: As part of the National Epidemiologic Survey on Alcohol and Related Conditions, 1600 adults who met lifetime *DSM-IV* criteria for BP-I ($n = 1172$) and BP-II ($n = 428$) were included. Individuals were evaluated using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-*DMS-IV* Version and data was analyzed from Waves 1 and 2, approximately 3 years apart.
Results: Sixty percent of individuals with BP had at least one lifetime comorbid anxiety disorder. Individuals with BP and anxiety disorders shared lifetime risk factors for major depressive disorder and had prospectively more depressive and manic/hypomanic episodes, suicidal ideation, suicide attempts, and more treatment seeking than those without anxiety. During the follow-up, higher incidence of panic disorder, drug use disorders, and lower psychosocial functioning were found in individuals with BP with versus without anxiety disorders.
Conclusions: Anxiety disorders are prospectively associated with elevated BP severity and BP-related mental health service use. Early identification and treatment of anxiety disorders are warranted to improve the course and outcome of individuals with BP.

1. Introduction

Clinical (Boylan et al., 2004; Henry et al., 2003; McElroy et al., 2001; Perlis et al., 2004; Pini et al., 1997) and epidemiological studies (Chen and Dilsaver, 1995a,b; Goodwin and Hoven, 2002; Kessler et al., 1997; Merikangas et al., 2007) have documented high rates of anxiety disorders among adults with bipolar disorder (BP) and provided compelling evidence that anxiety disorders may be the most prevalent psychiatric comorbidity among patients with BP, particularly BP-II (Cassano et al., 1999; Doughty et al., 2004; Henry et al., 2003; Perugi et al., 1999; Pini et al., 1997). For example, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (Perlis et al., 2004) found that 51% of 983 adults with BP had at least one comorbid lifetime anxiety disorder. Although a high prevalence of comorbid anxiety disorders is not unique to BP, some studies have shown that comorbid anxiety disorders are even more common in BP than in major depressive disorder (MDD) (Chen and Dilsaver, 1995a; Simon et al., 2003).

Recent studies have suggested that comorbid anxiety disorders are associated with worse course and outcome of individuals with BP (Boylan et al., 2004; Coryell et al., 2009; Gaudiano and Miller, 2005; Otto et al., 2006). Regarding clinical characteristics of BP with anxiety disorders, the literature suggests earlier onset of mood symptoms, greater severity of BP symptoms, increased prevalence of suicidal behavior, longer time to remission from affective episodes, and reduced duration of time spent euthymic (Boylan et al., 2004; MacQueen et al., 2003; Otto et al., 2006; Simon et al., 2004). Comorbid anxiety disorders among individuals with BP are also associated with greater prevalence of drug and alcohol use disorders (Goodwin and Hoven, 2002; MacQueen et al., 2003; Simon et al., 2004). Studies focusing on the treatment of individuals with BP have shown that comorbid anxiety is associated with worse response to mood-stabilizing medications, greater risk of medication-induced mania, and increased psychiatric polypharmacy (Feske et al., 2000; Henry et al., 2003; Pini et al., 2003). In addition, poor functional outcome and diminished quality of life

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(Albert et al., 2008; Bauer et al., 2005; Simon et al., 2004) have been related with comorbid anxiety in individuals with BP.

The majority of the above findings are derived from clinical samples, and epidemiologic studies are therefore needed to examine whether those findings extend to the general population of individuals with BP. Several epidemiologic studies confirm that comorbid anxiety disorders are exceedingly prevalent in BP (Angst, 1998; Chen and Dilsaver, 1995a,b; Goodwin and Hoven, 2002; Merikangas et al., 2007, 2011). However, to our knowledge, epidemiologic surveys have not examined the course and outcome of individuals with BP and anxiety disorders.

Previously reported cross-sectional data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) suggested that comorbid anxiety disorders confer increased liability toward poor mental health functioning and greater BP-related health service utilization (Goldstein and Levitt, 2008). Given the clinical relevance of anxiety and BP and the lack of longitudinal epidemiologic studies, we sought to assess prospectively for the first time the course and outcome of individuals with BP with versus without comorbid anxiety disorders in a large, nationally representative epidemiologic study, the NESARC.

The aim of this study was to examine the prevalence and correlates of comorbid anxiety disorders among individuals with BP and their association with prospectively ascertained comorbidities, treatment, and psychosocial functioning. We hypothesized that as compared with individuals with BP and no comorbid anxiety disorders, those with BP and a comorbid anxiety disorder would have: (1) more severe lifetime BP symptoms, (2) greater proportion of new onset of comorbidities, (3) higher rates of treatment seeking, and (4) lower psychosocial functioning.

2. Material and methods

The NESARC (Grant et al., 2005a, 2003b) is a longitudinal nationally representative survey based on the civilian, non-institutionalized population of the 50 United States, age 18 and over. Data collection was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and was conducted in two waves using face-to-face interviews. Wave 1 interviews ($n = 43{,}093$) were conducted between 2001 and 2002 by trained lay-interviewers who had an average of five years experience working on census and other health-related national surveys (Grant et al., 2003b). The current study utilized data from Wave 1 as well as Wave 2 interviews, which were conducted between 2004 and 2005 with 34,653 of the NESARC Wave 2 respondents (Grant et al., 2005a). After accounting for those ineligible for the Wave 2 interview, the response rate for Wave 2 was 86.7%. The mean interval between Wave 1 and Wave 2 interviews was 36.6 (SD = 2.62) months. The research protocol, including informed consent procedures, received full ethical review and approval from the U.S. Census Bureau and the U.S. Office of Management and Budget. Informed consent was obtained from all participants before beginning the interviews. Detailed descriptions of methodology, sampling, and weighting procedures can be found elsewhere (Grant et al., 2003b).

Respondents with lifetime diagnosis of BP-I ($n = 1172$) and BP-II ($n = 428$) in Wave 1 were included in the present study, and were divided into two groups for the purpose of analyses: individuals with lifetime BP and anxiety disorders (2.09%; $n = 725$) and individuals with BP without anxiety disorders (2.38%; $n = 875$).

2.1. Measures

Sociodemographic measures included age, sex, race/ethnicity, marital status, education, employment status and personal income.

All diagnoses were made according to DSM-IV criteria using the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-Version for DSM-IV (AUDADIS-IV), a valid, reliable, fully structured diagnostic interview designed for use by professional interviewers who are not clinicians (Grant et al., 2001). The AUDADIS-IV diagnoses of mood and anxiety disorders (Grant et al., 2005c) and substance use disorders (Grant et al., 2004) have demonstrated reliability and validity. Reliability of the BP-I diagnosis ($\kappa = 0.59$) is fair and good for BP-II ($\kappa = 0.69$) (Grant et al., 2005b), whereas the reliability is excellent for alcohol diagnoses ($\kappa \geq 0.74$) and drug diagnoses ($\kappa \geq 0.79$) (Grant et al., 2004). The anxiety disorders included in the present study are social anxiety disorder, panic disorder, and generalized anxiety disorder, which have fair to good reliability ($\kappa = 0.42$–0.52) (Grant et al., 2004).

The study further included variables considered risk factors for BP in individuals with versus without anxiety disorders that have been extensively studied in major depressive disorder (MDD) (Kendler et al., 2002, 2006), dysthymic disorder (Blanco et al., 2010), and generalized anxiety disorder (GAD) (Vesga-Lopez et al., 2008). For consistency with previous research, we queried about lifetime risk factors for depression initially proposed by Kendler and colleagues (Kendler et al., 2002, 2006), but which may increase the risk for anxiety disorders as well (Vesga-Lopez et al., 2008). In accordance with previous research (Vesga-Lopez et al., 2008) we organized the risk factors into 3 sets: (1) familial influences, including family history of depression, drug and alcohol use disorders; (2) risk factors with childhood onset, including parental loss before age 18, vulnerable family environment (defined as history of separation from a biologic parent before age 18), early onset of anxiety disorder (viz, before age 18), conduct disorder and low self-esteem (defined as present most of the time throughout their lives); and, (3) risk factors manifested into adulthood, including history of separation or divorce, low emotional reactivity, and social support.

We examined the clinical characteristics of BP (e.g., number and length of depressive and mania or hypomania episodes, recovery from depression and mania, suicidal ideation and suicide attempts) between Wave 1 and Wave 2 for individuals with BP with versus without anxiety disorders. In addition, we examined the treatment of BP (sought counseling, medication, any other treatment, hospitalized and attended to the emergency room) for major depressive (MDE) and mania or hypomania episodes between Wave 1 and Wave 2 for individuals with BP with versus without anxiety disorder. Incidence of comorbidities (alcohol or drug abuse/dependence, nicotine dependence, panic disorder, SAD, and/or GAD) was defined as developing a new disorder between Wave 1 and Wave 2.

Psychosocial functioning was assessed in both waves with the mental component summary of the 12-item Short Form Health Survey, version 2 (SF-12), a reliable and valid measure of disability used in population surveys (Ware et al., 2005). We also examined the 14 items of the Social Readjustment Rating Scale (e.g., move or anyone new living with, fired from job, unemployment, trouble or change work) (Holmes and Rahe, 1967) in the 12 month preceding Wave 2.

2.2. Statistical analyses

Statistical analyses were performed using SUDAAN to adjust for the complex design of the NESARC. Weighted percentages and means were computed to derive associations with prospectively ascertained comorbidities, treatment, and mental functioning among respondents with and without a comorbid anxiety disorders among individuals with BP. Standard errors and 95% confidence intervals (CIs) for all analyses were estimated computed and

because the combined standard error of 2 means (or percentages) is always equal to or less than the sum of the standard errors of those 2 means, we conservatively consider that two CIs that share a boundary or do not overlap to be significantly different from one another (Agresti, 2002). Odds ratios (ORs) for clinical characteristics of BP, new onset of comorbidities and treatment for BP were adjusted for age, sex, race and income. All *p*-values are based on two-tailed tests with $\alpha = 0.05$.

3. Results

3.1. Prevalence and sociodemographic correlates

Sixty percent of individuals with BP met lifetime criteria for at least one comorbid lifetime anxiety disorder (51.5% GAD, 47.8% social anxiety disorder, and 53.4% panic disorder) and 40% had 2 or more lifetime anxiety disorders. The age of onset of BP was not significantly different between individuals with versus without anxiety disorders (Mean ± SE, 25.33 ± 0.55 vs. 24.03 ± 0.5, $F = 3.14$, $p = 0.08$). The age of onset of anxiety disorders preceded the age onset of BP in individuals with both disorders (22.14 ± 0.59 vs. 25.33 ± 0.55). In addition, the age of onset of substance use disorders (SUD) was not significantly different between individuals with versus without anxiety (21.28 ± 0.47 vs. 21.55 ± 0.43, $F = 0.17$, $p = 0.68$).

As shown in Table 1, individuals over 30 years of age had greater odds of having BP with anxiety disorders than those aged 19–29 years. Women and unemployed individuals had greater odds of BP with anxiety disorders. Blacks and Hispanics had lower odds, whereas Native Americans had greater odds of lifetime BP with anxiety disorders compared to Whites. Widowhood, separation or divorce increased the odds of BP with anxiety disorders when compared to being married, whereas having never been married decreased the odds of BP with anxiety disorders. In addition, we found that the number of years with BP increased the risk of lifetime prevalence of anxiety disorders (OR = 1.03; 95% CI = 1.01–1.04, *p*-value = 0.0006).

3.2. Risk factors

The odds of family history of depression and substance use disorders were significantly greater for BP with versus without anxiety disorders. Individuals with BP and anxiety disorders were more likely to have been exposed to childhood risk factors, such as vulnerable family environment, and low self esteem than those without anxiety disorders. Social support and history of divorce or loss of spouse were the adult risk factors associated with anxiety among individuals with BP (Table 2).

3.3. Clinical characteristics of BP and mental health treatment

Individuals with BP and anxiety disorders were significantly more likely than those without anxiety disorders to have BP-I versus BP-II (Table 3). Individuals with BP and anxiety disorders had greater adjusted odds for any depressive and manic/hypomanic episodes, greater number of depressive and manic/hypomanic episodes, and higher rates of suicidal ideation and suicide attempts between Wave 1 and Wave 2 compared to those without anxiety disorders (Table 3). Regarding mental health treatment, adjusted odds for sought counselor, medication, and any treatment, for both depression and mania/hypomania, were significantly greater for BP with versus without anxiety disorders. Furthermore, individuals with BP and anxiety disorders had significantly more emergency room visits for depression (Table 3).

Table 1
Sociodemographic characteristics for lifetime BP with versus without anxiety disorders.

	BP with anxiety		BP without anxiety		OR	95%CI	*p*-value
	N = 725; % = 2.09		*N* = 875; % = 2.38				
	%	SE	%	SE			
Age							
18–29	27.13	2.18	43.13	2.33	1.00	1.00–1.00	0.0001
30–44	39.00	2.45	31.83	1.97	1.95	1.42–2.68	
45–64	29.55	2.03	21.35	1.67	2.20	1.60–3.03	
65+	4.31	0.75	3.69	0.71	1.86	1.06–3.25	
Sex							
Male	38.73	2.18	49.52	2.16	0.64	0.49–0.84	0.002
Female	61.27	2.18	50.48	2.16	1.00	1.00–1.00	
Race							
White	75.08	2.12	67.46	2.48	1.00	1.00–0.47	0.002
Black	9.68	1.11	13.65	1.34	0.64	0.65–0.44	
Native American	5.05	1.29	3.34	0.81	1.36	0.37–1.00	
Asian	2.74	0.99	2.92	0.86	0.84	0.86–2.83	
Hispanic	7.46	1.26	12.64	1.83	0.53	1.61–0.75	
Marital Status							
Married/cohabiting	52.41	2.13	48.67	2.00	1.00	1.00–1.03	0.0002
Widowed/separated/divorce	22.99	1.73	15.36	1.17	1.39	0.47–1.00	
Never married	24.60	2.07	35.97	2.04	0.64	1.88–0.86	
Education							
Less than high school	18.64	1.85	17.41	1.60	1.14	0.82–0.85	0.5
High school graduate	30.49	2.17	28.54	1.95	1.14	1.00–1.58	
Some college or higher	50.88	2.36	54.06	1.97	1.00	1.52–1.00	
Employment Status							
Employed	60.24	2.21	67.18	1.84	1.00	1.00–1.09	0.009
Unemployed	39.76	2.21	32.82	1.84	1.35	1.00–1.68	
Personal Income							
0–19,999	60.86	2.29	56.55	2.02	1.00	1.00–1.00	0.4
20,000–34,999	20.32	1.80	23.93	1.72	0.79	0.59–1.06	
35,000–69,999	14.99	1.62	16.18	1.48	0.86	0.60–1.23	
≥70,000	3.83	0.83	3.34	0.74	1.06	0.58–1.96	

Table 2
Risk factors for lifetime BP with versus without anxiety disorders.

	BP with anxiety		BP without anxiety		OR	95%CI	*t*	*p*-value
	N = 725; % = 2.09		*N* = 875; % = 2.38					
	% or mean	SE	% or mean	SE				
Family history								
Depression	74.56	2.21	67.09	1.99	1.44	1.06–1.94		0.02
Alcohol problems	62.14	2.19	51.34	1.99	1.56	1.22–1.99		0.0005
Drug problems	39.20	2.13	32.58	1.99	1.33	1.03–1.72		0.03
Childhood								
Parental loss	10.53	1.39	8.31	1.05	1.30	0.87–1.94		0.2
Vulnerable family environment	5.20	0.21	4.18	0.20			3.46	0.0001
Early onset of anxiety disorders	47.26	0.36	0.00	0.00			11.87	<0.0001
Conduct disorder	2.28	0.62	1.99	0.55	1.15	0.52–2.56		0.7
Low self-esteem	45.17	2.23	25.46	1.85	2.41	1.86–3.14		<0.0001
Adult								
Social support	20.06	0.33	18.35	0.21			4.34	0.0001
History of divorce/loss spouse	42.50	2.22	30.46	1.80	1.69	1.31–2.17		0.0002
Low emotional reactivity	25.07	2.03	26.28	1.88	0.94	0.71–1.24		0.6

3.4. Incidence of comorbidities

Adjusted odd showed significantly higher incidence of panic disorder and more drug use disorders in individuals with BP with versus without anxiety disorders (Table 3).

3.5. Mental functioning and social readjustment

Individuals with BP with versus without anxiety disorders had significantly lower scores on mental health scale comparison in Wave 1 and Wave 2, indicating greater disability on mental functioning (Fig. 1).

Table 3
Clinical characteristics, new onset of comorbidities, and treatment for lifetime BP with versus without anxiety disorders since wave 1.

	BP with anxiety *N* = 725; % = 2.09		BP without anxiety *N* = 875; % = 2.38		AOR[a]	95%CI[a]	*t*[a]/Wald Chi Sq[a]	*p*-value[a]
	% or mean	SE	% or mean	SE				
Clinical Characteristics of BP								
BP subtype								
BP-I	78.03	1.88	70.54	1.90	1.37	1.03–1.83	4.95	0.03
BP-II	21.97	1.88	29.46	1.90	1(ref)			
Any MDE	54.58	2.23	39.19	2.05	1.39	1.33–2.24	2.25	<0.0001
Number of MDE	3.37	0.24	2.76	0.16			1.45	0.03
Length of MDE (week)[b]	11.85	1.20	9.94	1.12				0.2
Recovery from depression	71.78	4.92	84.60	4.64	0.47	0.18–1.19		0.1
Any manic/hypomanic episodes	41.46	2.30	29.5	1.99	1.83	1.35–2.48	2.59	<0.0001
Number of manic/hypomanic episodes	3.63	0.25	2.72	0.29			1.02	0.01
Length of mania (week)[b]	6.30	0.98	5.31	5.31				0.3
Recovery from mania	73.64	4.56	79.68	4.73	0.71	0.33–1.52		0.4
Attempted suicide	8.57	1.84	6.08	1.65	1.56	0.74–3.30		0.2
Suicidal ideation	35.67	2.80	25.74	3.08	1.66	1.07–2.57		0.02
Lifetime suicide attempt	27.85	2.68	18.74	2.61	1.64	1.05–2.56	0.5	0.03
Earliest suicide attempt	23.66	1.33	24.12	2.31			0.24	0.6
Recent suicide attempt	30.84	1.85	31.19	2.29				0.8
New Onset of Comorbidites								
Any Anxiety Disorders	16.89	1.63	16.08	1.50	1.04	0.74–1.48		0.8
PANIC	11.99	2.11	4.27	1.15	3.37	0.99–5.70		<0.001
SAD	9.25	1.93	6.48	0.97	1.64	0.92–2.94		0.09
GAD	12.63	1.76	9.35	0.69	1.34	0.88–2.06		0.2
Alcohol Use Disorders	12.59	2.06	20.15	2.05	0.76	0.49–1.17		0.2
Drug Use Disorders	9.46	1.60	6.74	1.11	1.76	1.07–2.88		0.02
Nicotine Dependence	6.95	1.85	7.81	1.34	0.98	0.50–1.94		0.9
Treatment for BP								
Counselor for MDE	51.61	3.09	32.42	3.18	2.01	1.35–3.00		0.0005
Hospitalized for MDE	13.25	2.15	7.92	1.80	1.75	0.94–3.29		0.07
Emergency room for MDE	15.21	2.40	7.29	1.72	2.29	1.21–4.34		0.01
Medication for MDE	51.90	3.10	34.27	3.36	1.87	1.24–2.84		0.003
Sought any treatment for MDE	59.79	3.03	39.73	3.25	2.05	1.38–3.06		0.0003
Counselor for mania/hypomania	33.66	3.59	17.78	3.02	2.02	1.08–3.78		0.03
Hospitalized for mania/hypomania	6.41	2.01	4.73	1.45	1.56	0.57–4.30		0.4
Emergency room for mania/hypomania	6.45	1.96	3.93	1.33	1.86	3.06–3.78		0.3
Medication for mania/hypomania	33.93	3.20	18.24	2.99	1.99	1.15–3.43		0.01
Sought any treatment for mania/hypomania	40.94	3.44	22.92	3.40	2.04	1.18–3.56		0.01

Abbreviations: BP = Bipolar Disorder, BP-I= Bipolar Disorder I, BP-II = Bipolar Disorder II, MDE = Major Depressive Episode, SAD = Separation Anxiety Disorder, GAD = Generalized Anxiety Disorder.

[a] AOR is adjusted by age, gender, race and income.

[b] longest duration.

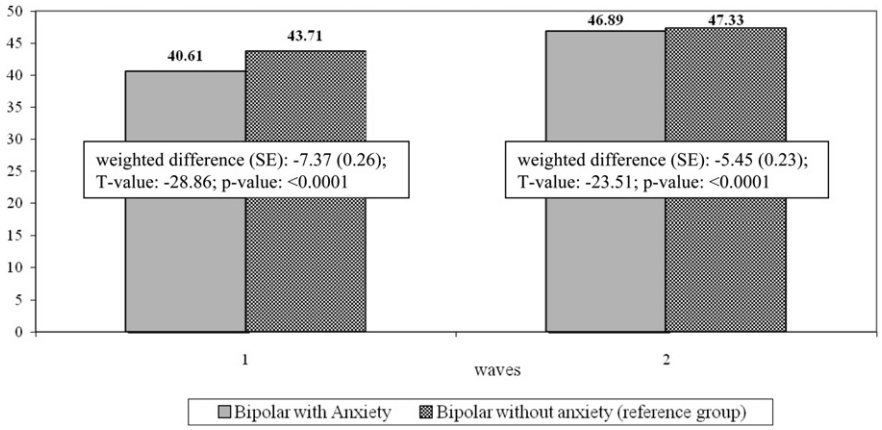

Fig. 1. Mental health scale comparison between groups in wave 1 and wave 2.

In addition, individuals with BP with anxiety disorders had significantly more trouble at work (AOR = 1.55; 95%CI: 1.11–2.17; $p = 0.009$), more financial crisis (AOR = 1.43; 95%CI: 1.09–1,88; $p = 0.009$), more death of family or close friends (AOR = 1.31; 95%CI:1.01–1.71; $p = 0.04$), and more family/close friends have been physically assaulted (AOR = 1.83; 95%CI: 1.09–3.07; $p = 0.02$). There were not other significant differences in measures of social readjustment.

4. Discussion

In a large, nationally representative sample of US adults, 60% of individuals with BP had at least one comorbid anxiety disorder. Individuals with BP and anxiety disorders shared lifetime risk factors for MDD, and had more depressive and mania/hypomania episodes, suicidal ideation, suicide attempts, and higher rates of treatment-seeking than those without anxiety disorders. They also had higher incidence of panic disorder and drug use disorders, and poorer mental health functioning than individuals with BP without anxiety disorders.

The present findings are consistent with the high prevalence of comorbid anxiety disorders in previous clinical (Boylan et al., 2004; McElroy et al., 2001; Pini et al., 1997) and epidemiological (Chen and Dilsaver, 1995a,b; Kessler et al., 1997; Merikangas et al., 2011; Perlis et al., 2004; Szadoczky et al., 1998) studies of adults with BP. We found that individuals with BP and anxiety disorders were more likely to have a diagnosis of BP-I as did clinical (McElroy et al., 2001; Simon et al., 2004) and epidemiologic studies (Merikangas et al., 2011), contrary to other clinical studies in youth (Masi et al., 2007; Sala et al., 2010) and adults (Cassano et al., 1999; Doughty et al., 2004; Henry et al., 2003; Perugi et al., 1999). Recently, the National Comorbidity Survey Replication (NCS-R) (Merikangas et al., 2007) found no significant differences in comorbid anxiety disorders in BP-I versus BP-II (86.7% vs. 89.3%).

On average, the onset of anxiety disorders preceded the onset of BP in individuals with both disorders and supports the idea that anxiety disorders could be a risk factor for subsequent development of BP (Goldstein and Levitt, 2007). Interestingly, recent studies found that offspring of parents with BP had higher rates of anxiety disorders than offspring of control parents suggesting that anxiety may be a precursor of BP among BP offspring (Birmaher et al., 2009; Goldstein et al., 2010). At the same time, we found that the duration of years ill with BP increased the risk of lifetime prevalence of anxiety disorders. This raises the question of whether this could be a sensitization-like phenomenon occurring as a consequence of the progression of the BP.

Our findings converge with previous clinical studies showing that comorbid anxiety disorders among individuals worsen the course of BP, being associated with more major depressive (MDE) (Gaudiano and Miller, 2005; Mantere et al., 2010) and mania/hypomania episodes, suicidal ideation, and suicide attempts (Bauer et al., 2005; Simon et al., 2004, 2007; Young et al., 1993). In addition, we found higher rates of treatment-seeking for either MDE and mania/hypomania episodes, which may reflect the poor treatment response of these individuals (Feske et al., 2000; Frank et al., 2002; Henry et al., 2003; Pini et al., 2003) or the need of more treatment for the severity associated with comorbid anxiety disorders in BP. Furthermore, more emergency room visits for MDE were found confirming evidence of the severity of depressive episodes in individuals with BP and anxiety disorders (Gaudiano and Miller, 2005).

Individuals with BP and anxiety disorders had higher prevalence of several of the risk factors first identified by Kendler for depression (Kendler et al., 2002, 2006) and more recently by our group for GAD (Vesga-Lopez et al., 2008). Overall, these findings suggest that those factors may increase the risk for a broader range of disorders beyond depression. Recently, Mantere and colleagues (2010) (Mantere et al., 2010) found strong evidence for the concurrent and longitudinal association between anxiety and depressive but not manic symptoms in BP suggesting a probable manifestation of the same illness propensity.

Epidemiological as well as clinical studies have shown that adults (Chengappa et al., 2000; Grant et al., 2004) with BP are at high risk for SUD, and both BP and SUD are strongly associated with anxiety disorders (Goldstein and Levitt, 2008). Our findings also showed that individuals with BP and anxiety disorders had higher incidence of drug use disorders than those without anxiety, suggesting the possibility that early recognition and treatment of these individuals may prevent the development of drug use disorders. At the same time, we found that age onset of SUD preceded the age onset of BP and anxiety disorders in individuals with versus without anxiety suggesting that individuals with SUD might be at high risk to develop both disorders.

Furthermore, individuals with BP and anxiety disorders had higher incidence of panic disorder than those without anxiety disorders. This may reflect continuity of anxiety disorders across diagnostic subtype (heterotypic continuity) (Costello et al., 2003; Ferdinand et al., 2007). Alternatively, the association of panic disorder and BP could be specific rather than mere realizations of larger processes involving both internalizing disorders (Kessler et al., 2011).

Confirming evidence of previous studies (Bauer et al., 2005; Boylan et al., 2004; McElroy et al., 2001; Otto et al., 2006),

individuals with BP and anxiety showed poorer psychosocial functioning. These individuals can experience work, family and social impairment and be made to contend with increased health care costs and strains on family support (Post, 2005).

The present findings might suggest that BP and anxiety disorders are disorders with overlapping pathophysiological mechanisms, as suggested by their high rate of co-occurrence (Angst, 1998; Chen and Dilsaver, 1995a,b; Kessler et al., 1994), shared genetic variance (MacKinnon et al., 1998; Wozniak et al., 2002), shared biological mechanisms including heightened noradrenergic and dopaminergic activity (Freeman et al., 2002; McElroy et al., 2001), and neuroimaging studies showing amygdala volume reductions in adults with anxiety disorders (Rauch et al., 2003) and BP (Blumberg et al., 2003).

Taken together, the above-noted findings indicate that anxiety disorders may uniquely contribute to BP severity independently of other common comorbidities such as SUD (Goldstein and Levitt, 2008; McElroy et al., 2001). The greater persistence of anxiety disorders over time, particularly in individuals with more severe anxiety (Sala et al., in press) may explain in part the high association between anxiety disorders and BP and could be a unique factor that negatively influences BP severity and prognosis (Coryell et al., 2009; Gaudiano and Miller, 2005; Otto et al., 2006). These findings are clinically relevant because currently the first line pharmacological treatment for anxiety disorders, in the absence of BP, are the selective serotonin reuptake inhibitors (SSRIs) (Bandelow et al., 2002; Kasper et al., 2005), which may trigger or destabilize BP symptoms (Ghaemi et al., 2003). However, there have been very few double-blind, controlled trials examining the treatment response of individuals with BP and anxiety disorders (Kauer-Sant'Anna et al., 2009; Rakofsky and Dunlop, 2011). Cognitive-behavioral therapy (CBT) for example, has been shown to be highly effective in anxiety disorders and in BP (Lam et al., 2003), but no studies to our knowledge have examined CBT for anxiety in BP specifically. From a clinical standpoint, our findings highlight the importance of early targeting anxiety disorders, and the need for implementing/developing effective psychotherapeutic approaches that treat anxiety in individuals with BP. Focusing on the treatment of comorbid anxiety disorders may lessen the negative clinical course and psychological functioning of those subjects with BP. Further studies examining specific interventions for anxiety disorders in BP are needed.

The potential limitations of this study should be taken into consideration. First, the NESARC interviews were conducted by lay professional interviewers rather than clinicians. However, the NESARC interviewers received extensive training with a highly structured and well-validated diagnostic assessment instrument (Grant et al., 2003a). Second, not all respondents from Wave 1 were able to be interviewed in Wave 2. Reasons for the decline included respondents who were deceased, institutionalized, or unwilling to participate at the time of the second interview. However, statistical adjustments were made for nonresponse. Furthermore, although not all respondents were available for re-interview, the response rate of Wave 2 was 86.7% (Grant et al., 2008), a much higher figure than other nationally representative surveys.

This study has also some important strengths. First, to our knowledge, this is the first nationally representative longitudinal study examining the course and outcome of individuals with BP and anxiety disorders. Second, it examined multiple specific anxiety disorders. Finally, we included in the study both BP-I and BP-II. Although most previous clinical studies (Bauer et al., 2005; Boylan et al., 2004; Henry et al., 2003; MacQueen et al., 2003; McElroy et al., 2001; Otto et al., 2006; Perlis et al., 2004; Pini et al., 1997; Simon et al., 2004, 2007; Young et al., 1993) included BP-II, to our knowledge few epidemiologic studies (Angst et al., 2005; Merikangas et al., 2007, 2011; Perlis et al., 2004) examining anxiety comorbidity in BP did so.

In summary, this study showed that anxiety disorders are highly prevalent among individuals with BP and are prospectively associated with elevated BP severity and BP-related health service use. In addition, our study extended previous findings by demonstrating that anxiety disorders predicted the incidence of panic disorders, drug use disorders, and increased psychosocial impairment. These epidemiologic findings are important because they confirm that the association between anxiety disorders and illness severity in BP exists in unselected samples, and is not restricted to tertiary clinical settings in academic health science centers where many clinical samples are recruited. Given the clinical and treatment implications of these epidemiological findings and the additional contribution on previous clinical research in this field support that early identification and accurate diagnosis are warranted. Further studies examining specific interventions for anxiety in individuals with BP are needed.

Conflict of interest

Neither the National Institute on Alcohol Abuse and Alcoholism, nor NIH or the Alicia Koplowitz Foundation had further role in the study design; analysis and interpretation of data; in the writing of the manuscript and in the decision to submit the paper for publication.

Contributors

Dr. Sala managed the literature searches, analyses, and wrote the manuscript. Dr. Goldstein, Dr. Morcillo and Mrs. Castellanos review the manuscript. Mrs. Liu made the statistical analyses and Dr. Blanco designed the study, implementing quality assurance. All authors contributed to and have approved the final manuscript.

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