Bipolar Disorders 2006: 8: 665–676

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BIPOLAR DISORDERS

Review Article

Anxiety disorders and bipolar disorder: a review

McIntyre RS, Soczynska JK, Bottas A, Bordbar K, Konarski JZ, Kennedy SH. Anxiety disorders and bipolar disorder: a review. Bipolar Disord 2006: 8: 665–676. © Blackwell Munksgaard, 2006

Context: Epidemiological, clinical and familial studies indicate that anxiety disorders (ADs) are highly comorbid in persons with bipolar disorder (BPD). The phenomenological overlap between ADs and BPD is reported more frequently in individuals with female predominant bipolar presentations (e.g., bipolar II disorder). Anxiety comorbidity in the BPD population poses a serious hazard. For example, it is associated with an intensification of symptoms, non-recovery, substance use comorbidity and harmful dysfunction (e.g., suicidality).

Objective: The evidentiary base informing treatment decisions for the anxious bipolar patient is woefully inadequate. Several expert consensus and evidence-based treatment guidelines for BPD suggest various treatment avenues, although these have been insufficiently studied. The encompassing aim of this paper is to synthesize extant studies reporting on the co-occurrence of AD and BPD. Taken together, a compelling basis emerges for prioritizing the identification and management of anxiety symptomatology in the BPD population.

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Key words: anxiety – bipolar disorder – comorbidity

Received 25 July 2005, revised and accepted for publication 1 March 2006

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> *Obviously, obsessions are evolving in a paroxysmal mode. For intermittent obsessions I am convinced that they are in almost all cases a part of periodic psychosis.* (1,2)

Historical perspectives

Bipolar disorder (BPD) is a highly prevalent and heterogeneous disorder of multifactorial aetiology. The symptomatic course of BPD is highly recurrent, often chronic and associated with functional impairment and premature mortality (3, 4). Bipolar disorders are amongst the most costly psychiatric disorders in terms of total economic cost and loss to human capital (2, 5, 6).

Historically, anxious morbidity has been reported as a fundamental feature of BPD. For example, Kraepelin described mixed states of manic-depressive insanity as 'depressive or anxious mania… a morbid state… composed of flight of ideas, excitement, and anxiety… mood is anxiously despairing'. He also described 'excited depression… great restlessness… mood is anxious, despondent, lachrymose, irritable, occasionally mixed with a certain self-irony' (7, 8). Moreover, reports of obsessive–compulsive symptoms (OCS) complicating BPD first appeared in the 19th century, when Morel described patients with circular affective illnesses who had OCS admixed with depressive episodes (9, 10).

Comorbidity is defined as the co-occurrence of multiple disease entities with distinct aetiologies (11, 12). Hitherto, investigations describing comorbidity in BPD have frequently reported on the

RSMcI is a consultant for and/or has received speaker fees from Janssen, Eli Lilly & Co., AstraZeneca, Pfizer, Wyeth, GlaxoSmithKline, Bristol-Myers Squibb, Merck and Bioavail. JKS has received grant support from Janssen Ortho, Organon and Wyeth. AB has served on the speakers bureau of Eli Lilly, Canada and AstraZeneca. JZK has received grant support from Wyeth and Eli Lilly & Co. SHK has received research support from Pfizer, AstraZeneca, Organon and Boehringer Ingelheim; has served on the speakers bureau of Lundbeck, Organon, Wyeth-Ayerst and GlaxoSmithKline; and has served on the advisory boards of Pfizer, the Lundbeck Foundation, Eli Lilly & Co., GlaxoSmithKline and Servier. KB has no reported conflict of interest.

staggering prevalence and clinical implications of comorbid alcohol and substance use disorders (13). Recent investigations, however, provide compelling evidence that anxiety disorders (ADs) may be the most prevalent psychiatric comorbidity amongst persons with BPD (14–18). Moreover, anxiety comorbidity poses a serious hazard to individuals with BPD, i.e., it is associated with an intensification of symptoms, insufficient treatment response, non-recovery, poor functional outcome and suicidality (14, 17, 18).

This paper provides a synthesis of extant studies which report on the co-occurrence of AD and BPD. The review is organized into two broad categories: reports of anxiety comorbidity in persons who are diagnosed with BPD, and reports of bipolar comorbidity amongst persons whose principal diagnosis is an AD. Causal pathways, psychobiological mechanisms, and treatment recommendations for persons with co-occurring BPD and AD are comprehensively reviewed in companion papers published in this supplement.

Methods

A MEDLINE search was conducted of all English-language articles published between 1966 and July 2005. The search terms were: bipolar disorder (BPD), bipolar I disorder (BPDI), bipolar II disorder (BPDII) and major depressive disorder (MDD), cross-referenced with: anxiety disorder (AD), panic disorder (PD), agoraphobia (Ago), obsessive–compulsive disorder (OCD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), social phobia (SoP), specific phobia (SP), and comorbidity. The search was supplemented with a manual review of references. In this review significant denotes statistical significance at the $p < 0.05$ level.

The psychiatric consequences of anxious symptomatology

The index presentation of BPD is frequently characterized by an admixture of anxiety, depression and sleep disturbance (19). The ubiquity of anxiety in BPD challenges the fundamental assumption that anxiety is a 'comorbidity', rather than a core dimension of bipolar illness (13, 20). For example, Cassidy et al. rated BPDI patients (manic, $n = 204$, or mixed, $n = 33$), on 15 classic features of mania and four features related to dysphoric mood. It was reported that depressed mood factored positively with anxiety, guilt, mood lability, and suicide and negatively with euphoric mood (21). These data, which cohere with clinical experience, indicate that anxiety and bipolar symptoms are a typology with imprecise diagnostic boundaries.

The pernicious effect of AD comorbidity in major depressive disorder (MDD) is unambiguously reported. For example, a depressed patient with prominent anxiety symptoms would be expected to respond less favourably to pharmacological (or psychotherapeutic) treatment and pursue a highly recurrent illness course (22). Preliminary reports of the hazardous effects of anxiety in BPD indicate similar prognostic implications.

For example, Feske et al. examined the correlates of acute treatment response in BPDI patients ($n = 124$). Anxiety symptomatology was associated with a longer time to remission in both depression and mania. Moreover, non-remitting patients were more likely to report a history of panic attacks, current or past anxiety, more severe depression and a greater number of previous affective episodes. Patients reporting a history of panic attacks also required a higher mean number of medications to achieve symptomatic remission (23).

It is widely accepted that anxiety symptomatology in the unipolar depressed patient is associated with several indices of illness severity and suicidality (24). Young et al. reported that anxiety symptoms in BPD are also hazardous insofar as they are associated with concurrent cyclothymia, alcohol abuse and suicidal behaviour. It was also reported that highly anxious BPD patients exhibited a less favourable lithium response (25). The association of anxiety with suicidality, and less favourable treatment responses in BPD patients, has been consistently reported (26–28).

Poor insight in BPD is common, affected by illness phase, and predictive of treatment non-adherence and poor outcome (29–31). Pini et al. (32) preliminarily evaluated the effect of anxiety comorbidity on insight in BPD patients. Insight was measured with the Scale for Unawareness of Mental Disorders (SUMD). Persons with BPD and comorbid SoP or OCD had more favourable insight ratings than BPD persons with comorbid PD. It was also reported that the lifetime number of manic episodes and hospitalizations were relatively lower in BPD patients with comorbid SoP and OCD (32).

In summary, the disaggregation of BPD symptoms into their constituent domains reinforces the assertion that anxiety, in many patients, may be a core dimension of BPD. Moreover, the presence of anxiety is associated with suicidality, illness recurrence, hospitalization and poor insight. These preliminary conclusions call for specific attention to anxiety symptoms in the diagnosis and management of BPD.

Anxiety disorder comorbidity in bipolar disorder

Community-based epidemiological studies

Scrutinizing comorbid medical and psychiatric disorders exclusively in clinical samples is potentially limited by Berkson's bias (13). The reliability of lay interviewers diagnosing ADs in community-based samples is well established. In contradistinction, the reliability of identifying BPD cases with a predominantly mixed/dysphoric presentation (or bipolar spectrum) is not ideal with the currently available diagnostic interviews (33, 34). Clinical studies indicate that AD comorbidity may be more prevalent in mixed and 'softer' expressions of BPD, suggesting that community-based epidemiological studies may underestimate the prevalence of AD comorbidity in BPD subpopulations (33).

The National Comorbidity Survey (NCS) provides a stratified, multistage area probability sample of the non-institutionalized civilian population in the 48 conterminous United States. The estimated lifetime prevalence of any AD in BPD was estimated at 92.9% (odds ratio, OR = 31.2) versus 72.0% for alcohol abuse. Specific phobia was the most prevalent AD comorbidity (66.6%) while PD was the least prevalent (33.1%) (35).

The Epidemiologic Catchment Area (ECA) study was also a multistage, cross-national, epidemiological survey. The lifetime prevalence of OCD and PD amongst persons with BPD and MDD was estimated by analysing the ECA study database. The lifetime rates of OCD were significantly higher in the BPD versus the MDD group (21.0% and 12.8%, respectively, versus 2.5% in the general population). Furthermore, a significant association between comorbid OCD and suicidality was reported. The association between anxiety symptoms (and disorders) and suicidality in BPD is a consistent theme in the BPD literature (36, 37).

The comorbidity between PD and BPD is reported as highly significant in both epidemiological and familial studies (38). For example, an analysis of the ECA survey database also reported that the lifetime prevalence of PD was significantly higher amongst persons with BPD (20%) versus MDD (10.0%) and the general population (0.8%) (39). The extensive phenomenological overlap between PD and BPD suggests that BPD-PD may be a distinct subphenotype of BPD (38, 40–42).

Taken together, results from community-based epidemiological studies indicate that respondents screening positive for BPD are also more likely to screen positive for an AD. The odds ratio for all individual ADs is increased amongst BPD cases. The co-occurrence of AD in BPD populations is associated with suicidality and possibly an earlier age of onset of bipolar illness.

Clinical studies

Several investigations have reported on the prevalence of ADs amongst bipolar patients reporting to a psychiatric setting (Tables 1–3). Relatively few studies have reported on AD comorbidity in primary care settings. Rihmer et al. described the prevalence of AD comorbidity amongst primary care patients (n = 2,953) with a diagnosable mood disorder. The estimated prevalence of any comorbid AD was lowest amongst persons with BPDI and highest in the BPDII patient group. The prevalence of comorbid ADs for the MDD group was intermediary between the two BPD subgroups (43). It has been reported elsewhere that softer expressions of BPD are often camouflaged as anxious depression in the primary care setting (44).

The appearance of AD comorbidity may be affected by the phase and severity of BPD symptoms. For example, Dilsaver and Chen reported that SoP and PD presenting during a bipolar episode (intraepisodic SoP and PD) were prevalent and highly associated with suicidality, particularly in depressed states (45). The longitudinal course of BPD is comprised largely of pleomorphic subsyndromal affective symptoms (4). MacQueen et al. reported that the prevalence of any AD comorbidity in BPD was highest in subsyndromal states [i.e., subsyndromal (80.6%), syndromal (54%), and euthymic (38.6%)] (46), which may presage the significant impairment noted in these patients. These data suggest that in some patients, anxiety comorbidity is most pronounced at the extremes of affective excursions, while in others, anxiety may present primarily as an 'intermorbid' disturbance.

Gaudiano and Miller (47) evaluated comorbid ADs in BPD patients (n = 92), and their association with bipolar illness severity, historical illness variables, chronicity and treatment response. Patients were categorized on the basis of anxiety comorbidity; BPD with AD (BPD-AD, 22%) or without (BPD, 78%). Persons with BPD-AD, on average, were younger and more likely to be female. The BPD-AD group were also more likely to report severe depression, chronic illness course, and negative treatment outcomes, primarily in depression.

Henry et al. (48) also reported that AD comorbidity was associated with an earlier age of BPD

Table 1. Anxiety disorder comorbidity in bipolar disorder

Prevalence	Population	DSM	n	Author
Anxiety disorder				
Current: 38% Lifetime: 43%	I	IV	BPD = 348	Bauer et al. (2005) (15)
Current: 15%	O	III-R	BPDI = 92	Gaudiano and Miller (2005) (47)
56%	O	IV	BPD = 138	Boylan et al. (2004) (16)
12 month prevalence: 52%	C	IV	Total = 10,641 BPD (I or II) = 35 MDD = 40	Mitchell et al. (2004) (65)
Current: 31% Lifetime: 51%	O	IV	BPDI = 360 BPDII = 115	Simon et al. (2004) (28)
Lifetime: 24%	I	IV	BPD = 318 BPDI = 237 BPDII = 81	Henry et al. (2003) (48)
Lifetime: 61%	O	IV	BPDI = 70	Tamam and Ozpoyraz (2002) (66)
Current: 30% Lifetime: 42%	O	IV	BPDI = 239 BPDII = 49	McElroy et al. (2001) (19)
Past and current: 45% Lifetime: 23%	O	IV	BPDI = 124	Feske et al. (2000) (23)
Lifetime: 18%	O	III-R	BPD = 77	Strakowski et al. (1998) (12)
Lifetime: 79%	O	III-R	BPD = 24 MDD = 38 Dysthymia = 25	Pini et al. (1997) (67)
Lifetime: 93%	C	III-R	BPDI = 59	Kessler et al. (1997) (33)
Lifetime: 16%	I	III-R	BPD = 71	Keck et al. (1995) (68)
24% (highly anxious)	O	*	BPD (I or II) = 81	Young et al. (1993) (25)
Past year: Euthymic 38.6% Subsyndromal 80.6% Syndromal 53.4%	O	IV	BPD = 138	MacQueen et al. (2003) (46)
Lifetime: 47.5%	O	IV	Total = 1,000 BPDI = 71% BPDII = 24% BPD NOS = 4% Other = 1%	Kogan et al. (2004) (50)
Familial: 29%	F	III-R	BPD = 603	MacKinnon et al. (2003) (40)
48.8%	C	III-R/IV	Hypomania = 41	Angst (1998) (57)
Generalized anxiety disorder				
31%	O	IV	BPD = 138	Boylan et al. (2004) (16)
12 month prevalence: 25%	C	IV	Total = 10,641 BPD (I or II) = 35 MDD = 4	Mitchell et al. (2004) (65)
Current: 2% Lifetime: 18%	O	IV	BPDI = 360 BPDII = 15	Simon et al. (2004) (28)
Lifetime: 27%	O	IV	BPD = 122 MDD = 114	Simon et al. (2003) (51)
Lifetime: 5%	O	III-R	BPD = 33 MDD = 97	Goodwin et al. (2002) (53)
Current: 3% Lifetime: 3%	O	IV	BPD (I or II) = 288	McElroy et al. (2001) (19)
Lifetime: BPDI 10.5% BPDII 21%	C	III-R	BPDI = 95 BPDII = 24 MDD = 443	Rihmer et al. (2001) (43)
Lifetime: 43%	C	III-R	BPDI = 59	Kessler et al. (1997) (33)
Lifetime: 32%	O	III-R	BPD = 24 MDD = 38 Dysthymia = 25	Pini et al. (1997) (67)
Lifetime: 0.04%	O	IV	BPDI = 124	Feske et al. (2000) (23)
Past year: Euthymic 15.9% Subsyndromal 52.8% Syndromal 29.3%	O	IV	BPD = 138	MacQueen et al. (2003) (46)
Phobia				
Lifetime (Ago, SoP, SP): 11%	I	IV	BPD = 318 BPDI = 237 BPDII = 81	Henry et al. (2003) (48)

Table 1. Continued

Prevalence	Population	DSM	n	Author
Agoraphobia				
Lifetime: 62%	C	III-R	BPDI = 59	Kessler et al. (1997) (33)
Lifetime: BPDI = 22% BPD II = 38%	C	III-R	Total = 2,953 BPDI = 95 BPDII = 24 MDD = 443	Rihmer et al. (2001) (43)
12 month: 6%	C	IV	Total = 10,641 BPD (I or II) = 35 MDD = 40	Mitchell et al. (2004) (65)
7.3%	C	III-R/IV	Hypomania = 41	Angst (1998) (57)
Specific phobia				
Lifetime: 67%	C	III-R	BPDI = 59	Kessler et al. (1997) (33)
Lifetime (simple phobia) BPDI = 10% BPDII = 17%	C	III-R	BPDI = 95 BPDII = 24 MDD = 443	Rihmer et al. (2001) (43)
(Simple phobia) 2%	O	III-R	BPDI = 129	Vieta et al. (2001) (69)
Lifetime: 26%	O	IV	BPDI = 70	Tamam and Ozpoyraz (2002) (66)
Lifetime: (Simple phobia) 5%	O	III-R	BPD = 24 MDD = 38 Dysthymia = 25	Pini et al. (1997) (67)
(Simple phobia) 10.3%	C	III-R/IV	Hypomania = 41	Angst (1998) (57)
Current: 8% Lifetime: 10%	O	IV	BPD (I or II) = 288	McElroy et al. (2001) (19)
Lifetime: 20%	O	IV	BPD = 122 MDD = 114	Simon et al. (2003) (51)
Lifetime: 17%	O	III-R	BPD = 33 MDD = 97	Goodwin et al. (2002) (53)
Lifetime: 16%	I	IV	BPD = 318 BPDI = 237 BPDII = 81	Henry et al. (2003) (48)
10%	O	IV	BPD = 138	Boylan et al. (2004) (16)
Lifetime: 0.04%	O	IV	BPDI = 124	Feske et al. (2000) (23)
Past year: Euthymic 4.5% Subsyndromal 19.4% Syndromal 8.6%	O	IV	BPD = 138	MacQueen et al. (2003) (46)
Social phobia				
Lifetime: 47%	C	III-R	BPDI = 59	Kessler et al. (1997) (33)
Lifetime: BPDI = 4.2% BPDII = 12.5%	C	III-R	BPDI = 95 BPDII = 24 MDD = 443	Rihmer et al. (2001) (43)
12 month prevalence: 19%	C	IV	10,641 BPD (I or II) = 35 MDD = 40	Mitchell et al. (2004) (65)
2%	O	III-R	BPDI = 129	Vieta et al. (2001) (69)
Lifetime: 20%	O	IV	BPDI-R = 70	Tamam and Ozpoyraz (2002) (66)
Lifetime: 31%	O	IV	BPD = 122 MDD = 114	Simon et al. (2003) (51)
Current: 13% Lifetime: 22%	O	IV	BPDI = 360 BPDII = 115	Simon et al. (2004) (28)
Lifetime: 10%	O	III-R	BPD = 33 MDD = 97	Goodwin et al. (2002) (53)
Current: 13% Lifetime: 16%	O	IV	BPD (I or II) = 288	McElroy et al. (2001) (19)
Lifetime: 29%	I	III-R	BPDI-M = 25 BPDI-DM = 19	Dilsaver and Chen (2003) (45)
17%	O	IV	BPD = 138	Boylan et al. (2004) (16)
Lifetime: 0.02%	O	IV	BPDI = 124	Feske et al. (2000) (23)
Past year: Euthymic 9.1% Subsyndromal 22.2% Syndromal 20.7%	O	IV	BPD = 138	MacQueen et al. (2003) (46)
9.8%	C	III-R/IV	Hypomania = 41	Angst (1998) (57)

Table 1. Continued

Prevalence	Population	DSM	n	Author
Panic disorder				
Lifetime: 33%	C	III-R	BPDI = 59	Kessler et al. (1997) (33)
Lifetime: 38%	I	III-R	BPDI-M = 25 BPDI-DM = 19	Dilsaver and Chen (2003) (45)
Lifetime: 21%	C	III	BPD = 167 MDD = 796	Chen and Dilsaver (1995) (39)
Lifetime: BPDI = 7.4% BPDII = 13%	C	III-R	BPDI = 95 BPDII = 24 MDD = 443	Rihmer et al. (2001) (43)
12 month prevalence: 26%	C	IV	10,641 BPD (I or II) = 35 MDD = 40	Mitchell et al. (2004) (65)
Lifetime: 2%	O	III-R	BPDI = 129	Vieta et al. (2001) (69)
Lifetime: 37%	O	III-R	BPD = 24 MDD = 38 Dysthymia = 25	Pini et al. (1997) (67)
Current: 8% Lifetime: 20%	O	IV	BPD (I or II) = 288	McElroy et al. (2001) (19)
Current: 8% Lifetime: 17%	O	IV	BPDI = 360 BPDII = 115	Simon et al. (2004) (28)
Lifetime: 16%	O	IV	BPD = 165 MDD = 83	Doughty et al. (2004) (70)
Lifetime: 27%	O	III-R	BPD = 33 MDD = 97	Goodwin et al. (2002) (53)
Lifetime: 16%	I	IV	BPD = 318 BPDI = 237 BPDII = 81	Henry et al. (2003) (48)
Lifetime: 4%	I	IV	BPD = 138 MDD = 87 SZ = 138	Craig et al. (2002) (71)
27%	O	IV	BPD = 138	Boylan et al. (2004) (16)
Current: 17% Lifetime: 20%	I	IV	BPD = 348	Bauer et al. (2005) (15)
Past year: Euthymic 22.7% Subsyndromal 47.2% Syndromal 17.2%	O	IV	BPD = 138	MacQueen et al. (2003) (46)
Familial: 17.7%	F	III-R	BPD = 606 (subjects)	MacKinnon et al. (2003) (40)
Familial: 18%	F	*	BPDI = 28 (families)	MacKinnon et al. (1998) (38)
27% (Panic attacks) Lifetime: 10%	O	IV	BPDI = 124	Feske et al. (2000) (23)
(Panic attacks) 31.7%	C	III-R/IV	Hypomania = 41	Angst (1998) (57)
Post-traumatic stress disorder				
Lifetime: 39%	C	III-R	BPDI = 59	Kessler et al. (1997) (33)
12 month prevalence: 11%	C	IV	Total = 10,641 BPD (I or II) = 35 MDD = 40	Mitchell et al. (2004) (65)
Current: 4% Lifetime: 7%	O	IV	BPD (I or II) = 288	McElroy et al. (2001) (19)
Lifetime: 0.05%	O	IV	BPDI = 124	Feske et al. (2000) (23)
Lifetime: 19%	O	IV	BPD = 122 MDD = 114	Simon et al. (2003) (51)
Current: 5% Lifetime: 17%	O	IV	BPDI = 360 BPDII = 115	Simon et al. (2004) (28)
Lifetime: 21%	O	III-R	BPD = 77	Strakowski et al. (1998) (12)
Lifetime: 11%	O	IV	Total = 426 BPDI = 102	Neria et al. (2002) (73)
Current: 40%	I/O	IV	Total = 275 BPD = 50 MDD = 65	Mueser et al. (1998) (52)
Lifetime: 17%	I	III-R	BPD = 71	Keck et al. (1995) (68)
15%	O	IV	BPD = 138	Boylan et al. (2004) (16)

Table 1. Continued

Prevalence	Population	DSM	n	Author
Current: 25% Lifetime: 28%	I	IV	BPD = 348	Bauer et al. (2005) (15)
Past year: Euthymic 4.5% Subsyndromal 22.2% Syndromal 17.2%	O	IV	BPD = 138	MacQueen et al. (2003) (46)
Obsessive–compulsive disorder				
Lifetime: 21%	C	III-R	BPDI = 59	Kessler et al. (1997) (33)
12 month prevalence: 10%	C	IV	Total = 10,641 BPD (I or II) = 35 MDD = 40	Mitchell et al. (2004) (65)
Lifetime: 2%	O	III-R	BPDI = 129	Vieta et al. (2001) (69)
Lifetime: 39%	O	IV	BPDI = 70	Tamam and Ozpoyraz (2002) (66)
Lifetime: 21%	O	III-R	BPD = 24 MDD = 38 Dysthymia = 25	Pini et al. (1997) (67)
Current: 8% Lifetime: 9%	O	IV	BPD (I or II) = 288	McElroy et al. (2001) (19)
Current: 6% Lifetime: 10%	O	IV	BPDI = 360 BPDII = 115	Simon et al. (2004) (28)
Lifetime: 16%	O	III-R	BPD = 77	Strakowski et al. (1998) (12)
Lifetime: 14%	O	III-R	BPD = 33 MDD = 97	Goodwin et al. (2002) (53)
Lifetime: 13%	O	IV	BPD = 122 MDD = 114	Simon et al. (2003) (51)
Lifetime: 10%	I	III-R	BPD = 71	Keck et al. (1995) (68)
Lifetime: 35%	I	III	BPD = 37 MDD = 105	Kruger et al. (1995) (11)
Lifetime: 4%	I	IV	BPD = 138 MDD = 87 SZ = 138	Craig et al. (2002) (71)
Lifetime: 3%	I	IV	BPD = 318 BPDI = 237 BPDII = 81	Henry et al. (2003) (48)
9%	O	IV	BPD = 138	Boylan et al. (2004) (16)
Past year: Euthymic 6.8% Subsyndromal 11.1% Syndromal 8.6%	O	IV	BPD = 138	MacQueen et al. (2003) (46)
5.1%	C	III-R/IV	Hypomania = 41	Angst (1998) (57)

Table adapted from Bauer MS, Altshuler L, Evans DR, Beresford T, Williford WO, Hauger R for the VA Cooperative Study #430 Team (15).
*Not stated.
O = outpatient, C = community, I = inpatient, F = familial; BPD = bipolar disorder; BPDI = bipolar I disorder; BPDII = bipolar II disorder; MDD = major depressive disorder; SZ = schizophrenia; BPDI-R = bipolar I disorder - remission; BPDI-M = bipolar I disorder - mania; BPDI-DM = bipolar I disorder - depressive mania.

onset. In addition, they reported that comorbid ADs were not associated with the total number of hospitalizations, presence of psychotic features, the likelihood of alcohol and substance abuse, suicidal behaviour, or lithium response. However, it was reported that the response to anticonvulsants was significantly lower in the BPD patients with anxious comorbidity.

Boylan et al. (16) also reported that BPD patients with comorbid AD had an earlier age of depression onset, higher frequency of rapid cycling, and a higher usage of benzodiazepine treatment. Moreover, patients with comorbid ADs had significantly higher rates of substance abuse or dependence, illness severity and chronicity, and evinced a lower mean Global Assessment of Functioning (GAF) score. Further analysis also indicated that GAD and PTSD were more likely to be associated with indices of poor BPD outcome (16). The association between ADs and alcohol abuse in BPD has been reported elsewhere (49). The association between anxiety and substance use disorders is an additional theme that emanates from the BPD literature.

McElroy et al. (19) reported anxiety (n = 122, 42%) and substance use disorders (n = 122, 42%) as the most frequent lifetime comorbid disorders in BPD. There was no significant difference in AD comorbidity between patients with BPDI and BPDII. The reported lifetime and current prevalences of 'any AD' was 42% and 30%, respectively.

Table 2. Bipolar disorder comorbidity in anxiety disorders

Comorbidity	Prevalence (%)	Population	DSM	n	Author
Social phobia					
BPD	4	*	III-R	57	Van Ameringen et al. (1991) (54)
BPDI	0	O	III-R	71	Perugi et al. (1999) (60)
BPDII	21	O	III-R	71	Perugi et al. (1999) (60)
	78 (in remission)	*	III-R	32 (18 in remission)	Himmelhoch (1998) (59)
BPD NOS	9	O	III-R	153	Perugi et al. (2001) (61)
Panic disorder					
BPD	88	F	*	Total = 528 PD = 41	MacKinnon et al. (1997) (41)
BPDI	2	*	III-R	140	Savino et al. (1993) (56)
	1	O	III-R	119	Perugi et al. (1999) (60)
BPDII	5	*	III-R	140	Savino et al. (1993) (56)
	5	O	III-R	119	Perugi et al. (1999) (60)
Panic attacks					
BPDI	21	F	*	BPDI = 28	MacKinnon et al. (1998) (38)
Obsessive–compulsive disorder					
BPDI	3	O	IV	628	Hantouche et al. (2003) (2)
	4	O	III-R	79	Perugi et al. (1999) (60)
BPDII	18	O	III-R	79	Perugi et al. (1999) (60)
	8	O	IV	628	Hantouche et al. (2003) (2)
Obsessive–compulsive disorder and major depressive disorder					
BPD	59	O	IV	68	Perugi et al. (2002) (64)
BPDI	32	O	IV	68	Perugi et al. (2002) (64)
BPDII	64	O	IV	68	Perugi et al. (2002) (64)
Panic disorder, obsessive–compulsive disorder and specific phobia					
BPDII	87	O	III-R	63	Perugi et al. (2001) (58)

*Not stated.
O = outpatient; C = community; I = inpatient; F = familial; BPD = bipolar disorder; BPDI = bipolar I disorder; BPDII = bipolar II disorder; BPD NOS = bipolar disorder not otherwise specified.

Lifetime Axis I comorbidity was associated with early age of onset of BPD symptoms, progressive severity of illness, and a family history of alcoholism and drug abuse. Current anxiety comorbidity was also associated with reduced occupational functioning, a history of rapid cycling, and a shortening of well intervals.

Simon et al. comprehensively evaluated the presence of anxiety and its correlates in a cross-sectional sample in the first 500 patients (BPDI n = 360, BPDII n = 115) enrolled in the Systematic Treatment Enhancement Program for BPD (STEP-BPD). The prevalences of any lifetime AD for the entire sample was 51.2% and 30.5%, respectively. Greater overall anxiety comorbidity was reported amongst patients with BPDI versus BPDII, reaching significance for the presence of at least one current AD, current PTSD and lifetime Ago (28, 50, 51).

The STEP-BPD participants exhibited a significantly higher prevalence rate for each individual AD than did the general population. The age of onset of BPD was significantly lower for patients with any lifetime AD than in patients without AD (15.6 versus 19.4 years, respectively). Patients with a lifetime AD also had less education, shorter time euthymic, lower rates of recovery and elevated rates of lifetime suicide attempt. It was also reported that bipolars with a comorbid AD had a higher prevalence of alcohol and substance use disorders. The presence of multiple ADs was independently associated with added impairment in quality of life and functioning. Converging with results from other studies, the presence of a lifetime AD was significantly associated with an increased number of suicide attempts (28, 51).

Simon et al. also sought to determine whether MDD (n = 114) and BPD (n = 122) could be distinguished by their differential associations with anxiety comorbidity, anxiety sensitivity and 'neuroticism'. In the univariate analysis, PD, OCD and GAD were more common among individuals with BPD compared with those with MDD. With the multivariate logistics model, a lifetime diagnosis of PD and current GAD were also both significantly more common among persons with BPD (51). Mueser et al. assessed the lifetime prevalence of traumatic events and DSM-IV-defined PTSD in patients (n = 275) with 'severe mental illness', which included BPD (n = 50). The rate of current PTSD was high in all groups: MDD (58%); schizoaffective disorder (57%); borderline personality disorder (54%); BPD (40%); other person-

Table 3. Correlates of anxiety disorder comorbidity in bipolar disorder

Comorbidity	Correlate	Author
Demographic correlates		
ADs	Lower SES	Strakowski et al. (1998) (12)
Current ADs	Women	Tamam and Ozpoyraz (2002) (66)
Lifetime anxiety	Less education	Simon et al. (2004) (28)
PTSD	Women	Strakowski et al. (1998) (12)
Clinical correlates		
Current AD	Less time euthymic	Simon et al. (2004) (28)
Current AD, GAD	More likely symptomatic, more eating disorders	MacQueen et al. (2003) (46)
Current or lifetime ADs	Lifetime substance disorder	Simon et al. (2004) (28)
Lifetime AD, panic, SoP, PTSD, GAD	Lower age of onset, suicide attempt history	Simon et al. (2004) (28)
Lifetime AD	More lifetime episodes, worse global psychopathology	Tamam and Ozpoyraz (2002) (66)
Lifetime AD	Lifetime substance disorder	Goodwin et al. (2002) (53)
Lifetime AD	More subsyndromal symptoms	MacQueen et al. (2003) (46)
Lifetime AD, Ago, PTSD	Type I	Simon et al. (2004) (28)
Lifetime panic, GAD, Ago, SP	Type II	Rihmer et al. (2001) (43)
Lifetime panic or anxiety symptoms	Earlier age of onset	Henry et al. (2003) (48)
OCD, current	Type II	Krüger et al. (2000) (74)
OCD, lifetime	Depressed/mixed > manic	Strakowski et al. (1998) (12)
OCD symptoms	Only during affective episodes	Strakowski et al. (1998) (12)
Panic, current	Depressed/mixed > manic	Dilsaver et al. (1997) (75)
Panic or anxiety symptoms, lifetime	Longer time to remission, more severe symptoms at intake, more depressive episodes, longer mixed/depressive episodes, more suicidality	Feske et al. (2000) (23); Frank et al. (2002) (72)
Panic or OCD symptoms	No relationship to affective status	Perugi et al. (2001) (58)
Panic, SoP, OCD, any AD	Mood instability	MacKinnon et al. (2003) (40)
PD, lifetime	Lifetime substance disorder	Goodwin and Hoven (2002) (76)
Non-OCD anxiety symptoms	No temporal relation to episodes	Strakowski et al. (1998) (12)
SoP	Decreases with hypomania	Perugi et al. (2001) (61)
Lifetime SoP, PD	Mixed states	Dilsaver and Chen (2003) (45)
Functional correlates		
Current AD, panic, Ago, SoP, PTSD, GAD	Lower role function and quality of life	Simon et al. (2004) (28)
Treatment correlates		
Panic or anxiety symptoms, lifetime	Increased intensity of medication treatment	Feske et al. (2000) (23)

Table adapted from Bauer et al. (2005) (15).
BPD = bipolar disorder; BPDI = bipolar I disorder; BPDII = bipolar II disorder; MDD = major depressive disorder; AD = anxiety disorder; PD = panic disorder; Ago = agoraphobia; OCD = obsessive–compulsive disorder; PTSD = post-traumatic stress disorder; GAD = generalized anxiety disorder; SoP = social phobia; SP = specific phobia; SES = socioeconomic status.

ality disorders (40%), and schizophrenia (28%) (52).

Bauer et al. examined the prevalence and the correlates of comorbid substance use disorders and ADs in a sample of veterans diagnosed with BPD (n = 348) receiving inpatient care in the US department of Veteran Affairs (VA). Anxiety disorders were associated with earlier age of onset, rapid cycling, higher probability of reporting depressive symptoms, higher rates of prior suicide attempts, and a greater number of prior-year depressive and manic episodes. Persons with comorbid ADs reported lower quality of life and higher severity of illness scores. The pernicious effect of ADs in BPD was particularly evident in persons with BPD who also had a substance abuse diagnosis (15). Goodwin et al. also described associations between anxiety and substance use disorders in BPD; comorbid AD was significantly associated with sedative and stimulant use disorders. It was also reported that panic attacks were associated with an increased prevalence of cocaine, sedative and stimulant use disorders (53).

Taken together, several conclusions can be drawn from the available data: ADs are highly comorbid in BPD patient populations; ADs appear to hasten the onset of overt BPD symptomatology; ADs are associated with multiple indices of poor outcome in BPD; the course characteristics between some ADs and BPD are overlapping;

and the presence of AD comorbidity is associated with other comorbidities in BPD (e.g., alcohol abuse), particularly in female patients.

Bipolar disorder comorbidity in anxiety disorder

Relatively fewer studies have reported the prevalence of BPDs amongst AD populations. Van Ameringen et al. (54) reported that the prevalence of BPD (3.5%) was not significantly increased amongst patients with SoP in contradistinction to MDD (70.2%). The estimated prevalence of bipolar spectrum disorders in the general population is approximately 2–4% (55). The prevalence of bipolar spectrum disorders may be higher amongst persons who report to a health care provider with a principal diagnosis of PD (i.e., BPDI, 2.1%; BPDII, 5%; cyclothymia, 6.4%) (56).

Previous research has reported that BPDI and BPDII were highly prevalent amongst patients whose principal diagnosis was an AD (PD, OCD and SoP). It was also reported that the mean age of onset of the AD was lowest in patients with comorbid SoP (versus comorbid OCD or PD). Anxiety (symptoms and disorders) are often a phenomenological antecedent to overt BPD; this calls for careful screening for BPD amongst paediatric patients reporting to health care providers with prominent anxiety symptoms (44, 57–59).

In a separate analysis, Perugi et al. also examined affective comorbidity in patients fulfilling criteria for PD, OCD and SoP. The rate of BPDII was more frequently associated with SoP (21.1%) and OCD (17.7%) than with PD (5.0%). The bipolar group also had a significantly higher number of lifetime comorbid ADs than persons without a principal mood disorder (60). Other reports have also described the association between bipolar spectrum comorbidity and SoP (61).

Indirect evidence supporting an increased prevalence of bipolar spectrum disorders among persons whose principal diagnosis is an AD is supported by treatment studies employing antidepressants. Antidepressant mobilization of hypomania, and/or the induction of mood instability have been reported in patients treated for OCD, GAD, PD and SoP (59). Anxious patients manifesting hypomanic symptoms or intensification of anxiety, in response to an antidepressant should be carefully screened for clinical presentations suggestive of BPD.

Conclusions

A significant concatenation of study results indicates that anxiety symptoms and disorders are ubiquitous in individuals with BPD. Anxiety phenomenology often precedes and may hasten the onset of overt BPD. Female-predominant forms of BPD (e.g., BPDII, mixed/dysphoric states and rapid cycling) appear more likely to manifest anxious comorbidity. Anxiety phenomenology in the individual with BPD is associated with several indices of harmful dysfunction (notably suicidality).

However, several unanswered questions remain regarding the specificity and mechanisms subserving the harmful effects of anxiety phenomenology (18). For example, BPD individuals with comorbid anxiety often meet criteria for one (or more) lifetime substance use disorders (SUD). Substance use disorders are highly prevalent comorbidities in BPD and are hazardous to the illness course and outcome (62, 63). A testable hypothesis is that the harmful effects of anxiety comorbidity are in part the consequence of SUD (28).

The ubiquity of anxiety symptoms in BPD challenges the assumption that BPD and AD are neurobiologically distinct disorders. It could be hypothesized that some BPD presentations may originate from a baseline of 'neurosis' (versus 'psychosis'). Taken together, a compelling basis emerges for prioritizing the identification and management of anxiety symptomatology in the BPD population.

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