

Illness Course, Comorbidity, Gender, and Suicidality in Patients With Bipolar Disorder

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Among patients with bipolar disorder, comorbid conditions are common. Comorbidity is associated with a more difficult course of illness (such as longer episodes, shorter time euthymic, and earlier age at onset) and an increase in related problems (such as suicidality and violence). Data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) reveal that anxiety disorders, attention-deficit/hyperactivity disorder, and substance and alcohol use disorder are conditions that commonly co-occur with bipolar disorder. This article details these findings and discusses the complications associated with these comorbid conditions. STEP-BD data about gender differences are also discussed, and correlates of suicidal ideation among patients entering the program are described. (*J Clin Psychiatry* 2006;67[suppl 11]:8–11)

Patients with bipolar disorder often experience comorbid conditions, including various anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and substance and alcohol abuse. In addition to providing statistical information about the course of bipolar disorder alone, the initial data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) have shown that course of illness can be greatly impacted and worsened by comorbidity. STEP-BD findings also reveal differences in course of illness and comorbidity according to gender differences and in suicidality according to course of illness and family and medical history.

COURSE OF ILLNESS

The early prospective findings of STEP-BD show some important trends in bipolar disorder course of illness. According to STEP-BD, among patients with bipolar disorder who met the criteria for recovery, approximately 5% of patients relapsed each month, and 80% of those relapses were to depression. The rate of psychiatric hospitalization was found to be 14.2/100 patient-years. The mortality rate was 0.11/100 patient-years, or 9 deaths including 2 suicides (G. S. Sachs, M.D., personal communication, January 2003).

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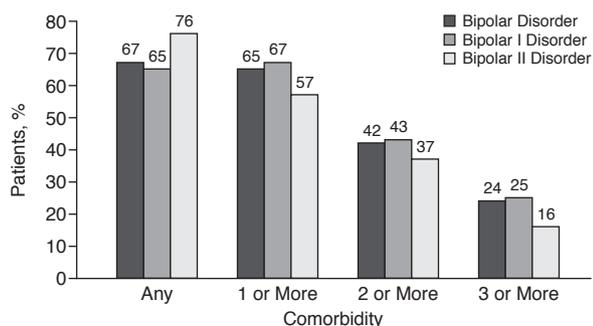
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COMORBIDITY

Comorbidity is common among patients with bipolar disorder. A study of Axis I comorbidity by McElroy and colleagues¹ found that 67% of all patients with bipolar disorder were experiencing a current comorbid condition, with 76% of patients with bipolar II disorder experiencing comorbidity (Figure 1). While 65% of all bipolar patients have experienced 1 or more lifetime comorbid conditions, 42% have experienced 2 or more lifetime comorbidities, and 24% have experienced 3 or more in their lifetimes. This high occurrence of comorbid conditions raises the question of whether the large number of misdiagnoses that patients with bipolar disorder often receive are actually comorbidities in some cases. A 2000 survey² by the National Depressive and Manic-Depressive Association found that 60% of patients with bipolar disorder had previously received a misdiagnosis of unipolar depression, and 26% had been previously misdiagnosed with anxiety disorders. Other common misdiagnoses included schizophrenia (18%), borderline or antisocial personality disorder (17%), alcohol abuse or dependence (14%), and schizoaffective disorder (11%).² Since comorbidity is the rule rather than the exception in patients with bipolar disorder, clinicians should look to previous diagnoses as perhaps comorbidities and not just misdiagnoses.

Conditions that co-occur with bipolar disorder can complicate the course of illness and lead to poorer outcomes. In patients with bipolar disorder, Vieta and colleagues³ found comorbidity in 31% and found it to be associated with higher numbers of mixed features, depressive episodes, and suicide attempts. Patients with comorbid disorders were also more likely to have depression as their initial episodes than patients without comorbidity.

Figure 1. Lifetime Comorbid Axis I Diagnoses in Patients With Bipolar Disorder^a



^aData from McElroy et al.¹

Studying Axis I psychiatric comorbidity, McElroy and colleagues¹ found earlier onset of bipolar disorder, earlier onset of affective symptoms, more severe episodes, and cycle acceleration to be significant indicators of lifetime and current comorbidity in patients with bipolar disorder. In patients with bipolar II disorder, Vieta and colleagues⁴ found that personality disorders (33%), substance abuse (21%), and anxiety disorders (8%) were common comorbid conditions. Comorbidity was significantly associated with suicidal ideation (in 74% of bipolar II patients with comorbidity versus 24% of bipolar II patients without comorbidity) and suicide attempts (45% vs. 5%, respectively).⁴

Anxiety

Anxiety disorders often occur at an elevated rate in patients with bipolar disorder, and the STEP-BD data from the first 500 participants revealed that about half of them experienced some type of lifetime anxiety disorder.⁵ Among patients with bipolar I disorder, 52.8% met the criteria for any anxiety disorder, while 46.1% of bipolar II patients entering the STEP-BD program were diagnosed with any anxiety disorder, including social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder (PTSD), panic disorder, obsessive-compulsive disorder (OCD), and agoraphobia (Figure 2).⁵

Comparing patients with bipolar disorder who had an anxiety disorder and those who did not, STEP-BD data showed that comorbid anxiety disorders increased the risk of suicide attempt. Among patients with any current anxiety disorders, 60.3% of patients had a history of suicide attempts, versus 27.4% of patients without current anxiety disorders.⁵ Suicide attempts were highest among patients with current comorbid PTSD (75.0%), panic disorder with or without agoraphobia (72.2%), and agoraphobia without panic disorder, although rates were high among other current anxiety disorders as well (generalized anxiety disorder [GAD], 62.1%; social anxiety disorder, 60.7%; OCD, 55.6%). Lifetime comorbid anxiety disor-

ders also substantially raised the rates of suicide attempt. While 22.1% of bipolar patients with no lifetime anxiety disorders had attempted suicide, the rate was 52.1% for patients with any lifetime anxiety disorder.

The age at onset for bipolar disorder is another aspect of the illness that is affected by comorbid anxiety disorders. The average age at onset of bipolar disorder for patients without any lifetime anxiety disorders was found to be 19.4 years.⁵ However, patients with any lifetime anxiety disorder experienced the onset of their first affective episode at 15.6 years old. Average age at onset was earliest for patients with social anxiety disorder (14.3 years), GAD (14.8 years), and agoraphobia without panic disorder (14.9 years).⁵

Comorbid anxiety disorders also affect the length of time spent euthymic in patients with bipolar disorder. Comparing the longest periods of euthymia, patients with no current anxiety disorder experienced 261 days of euthymia, while patients with any current comorbid anxiety disorder only experienced 113 days of euthymia.⁵ The shortest periods of euthymia were in patients with current comorbid agoraphobia without panic disorder (87 days), PTSD (95 days), social anxiety disorder (96 days), and GAD (97 days). Lifetime anxiety disorder also substantially reduced the number of days of euthymia. Patients without any lifetime anxiety disorder experienced 254 days of euthymia, compared with 183 days of euthymia in patients with any lifetime anxiety disorders.⁵

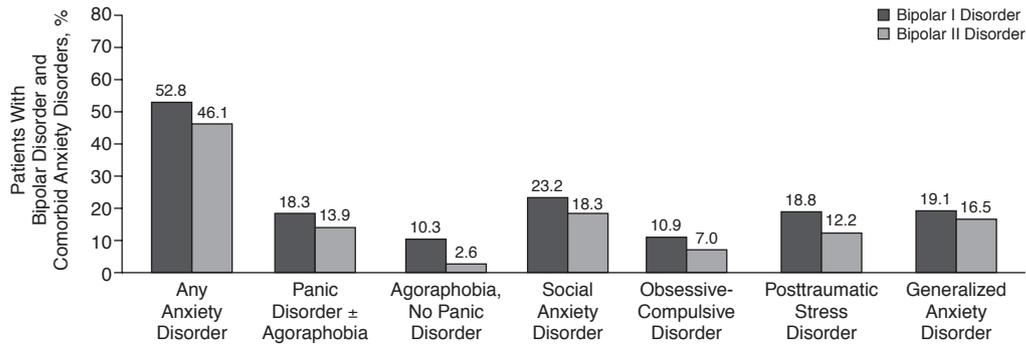
Attention-Deficit/Hyperactivity Disorder

Nierenberg and colleagues⁶ studied STEP-BD data from the first 1000 participants and found that 9.5% met criteria for a lifetime diagnosis of ADHD; 5.9% of the patients studied met criteria for full current ADHD, indicating that they had adult ADHD. Patients with lifetime ADHD were more likely to receive a diagnosis of bipolar I disorder than bipolar II disorder. Comorbidity with ADHD was found to increase the likelihood of another comorbid condition and confound and worsen the lifetime course of bipolar disorder.

Patients with ADHD and bipolar disorder showed a higher number of other psychiatric comorbid conditions than bipolar patients without ADHD.⁶ Agoraphobia without panic disorder, social phobia, PTSD, and GAD were significantly more common in patients with ADHD than in those without it. Alcohol and drug abuse or dependence were also significantly more likely to occur in patients with ADHD. All of these comorbid disorders were at least twice as likely to occur in ADHD patients as in patients without ADHD.

In addition to greater comorbidity, co-occurring ADHD in patients with bipolar disorder was associated with a more disabling and more chronic course of illness.⁶ ADHD patients were found to have an earlier age at onset of bipolar disorder than bipolar patients without lifetime

Figure 2. Anxiety Disorder Comorbidity in the First 500 Participants in STEP-BD^a



^aData from Simon et al.⁵

Abbreviation: STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

ADHD (13.9 years vs. 18.0 years). ADHD patients also experienced shorter periods of well time, shorter time between episodes, more episodes of mania and depression, and more days of irritability. Comorbid ADHD increased the reporting of legal troubles and histories of violence. Additionally, bipolar patients with comorbid ADHD were more likely to report a lifetime history of suicide attempts.

Substance and Alcohol Abuse

The STEP-BD⁷ data on substance abuse comorbidity in bipolar patients are generally consistent with most previous studies, which have found rates to be between 17% and 64% (Table 1).^{1,7-11} Among the first 500 participants in STEP-BD, 37% had comorbid substance abuse. For patients with bipolar disorder, a history of substance abuse can affect one’s ability to recover from an affective episode. Tohen and Zarate¹² reported a lower probability of recovery from the first episode for patients with substance abuse than for those without. After 2 months of an episode, patients without substance abuse had approximately a 65% rate of recovery, while little more than 40% of those with substance abuse had recovered. At 6 months, almost 90% of those without substance abuse had recovered, compared with only about 65% of those with substance abuse.

Compared with patients having 7 other types of psychiatric conditions (schizophrenia, antisocial personality disorder, phobia, panic disorder, OCD, major depression, and dysthymia), patients with bipolar I and bipolar II disorder had almost the highest lifetime rates of abuse or dependence on alcohol.^{13,14} Only patients with antisocial personality disorder had a higher rate of alcohol abuse and dependence (73.6%). While 16.5% of patients with major depression had received diagnoses of alcohol abuse or dependence, rates of alcohol abuse and dependence were 46.2% in patients with bipolar I disorder and 39.2% for bipolar II disorder.

Table 1. Substance Abuse Comorbidity in Patients With Bipolar Disorder

Study	Prevalence, %
McLean First Episode Mania Project, ⁸ 1992	17
Cincinnati Bipolar Project, ⁹ 1998	34
STEP-BD First 500 Participants, ⁷ 2001	37
Stanley Foundation Bipolar Network, ¹ 2001	42
Pittsburgh Cohort, ¹⁰ 2000	54
MUSC Cohort, ¹¹ 1991	64

Abbreviations: MUSC = Medical University South Carolina, STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

GENDER DIFFERENCES

In recent years, bipolar disorder research has increasingly focused on the differences in course of illness and comorbidity between men and women. While comorbidity is common in both men and women with bipolar disorder, there are differences in rates of comorbidity for some disorders. For example, among the first 500 STEP-BD participants,¹⁵ although 12.0% of women with bipolar disorder experienced comorbid bulimia, only 1.6% of men were diagnosed with it; similarly, more women (21.0%) than men (9.1%) had co-occurring PTSD. However, because these disorders are more common in women in the general population, these data do not indicate significant findings. Rates of other comorbid disorders in men versus women, including social phobia (20.0% vs. 23.0%), OCD (8.1% vs. 11.5%), and panic disorder (1.1% vs. 0.7%), were similar.

One interesting discovery from the STEP-BD data involved alcohol use among male and female bipolar patients. Men had a higher rate of lifetime alcohol abuse or dependence (42.0%) than women (32.0%).¹⁵ However, this represents a substantial change from another study¹⁶ that compared the rates of alcohol use disorders in bipolar patients versus the general population. That study found that men with bipolar disorder were 1.96 times more likely

to abuse or be dependent on alcohol than men without bipolar disorder, whereas women with bipolar disorder were 6.3 times more likely to have an alcohol use disorder than their counterparts in the general population.

In terms of the course of illness, many similarities existed between men and women in STEP-BD.¹⁵ Age at onset (17.2 years) was found to be the same, and the percentage of patients with a history of rapid cycling was similar (44.4% in men vs. 42.3% in women). The numbers of depressive and manic episodes were also similar for both genders. A trend was noted for men to present with mania as their first episode more often than women (28.4% vs. 20.9%), and women were slightly more likely than men to have depression at onset (57.2% vs. 49.2%).

Regarding problems associated with bipolar disorder, some differences were found between the genders. Men were more likely than women to have a history of violence (27% vs. 20%) and to have experienced legal problems (37% vs. 18%). Women were more likely to have a history of suicide attempts (45% vs. 27%).

SUICIDALITY

Using the STEP-BD data from the first 500 participants, researchers identified the clinical and demographic correlates of patients with suicidal ideation upon entry to the program.¹⁷ Of those patients entering the program with suicidal ideation, 60% had a history of suicide attempts, 46% had a history of alcohol abuse or dependence, and 35% had experienced a psychotic index episode. Suicidal ideation was also associated with having a first-degree relative with bipolar disorder (30%) and having a family history of suicide (11%). As discussed above, suicidality was also associated with having comorbid illnesses.⁴

Patients with suicidal ideation were also classified according to their clinical status.¹⁷ Half of these patients met the criteria for major depression, and 47% met the criteria for a mixed episode. Only 4.3% of suicidal patients were manic, and 16.1% had subsyndromal symptomatology. Interestingly, 4.9% of suicidal patients met the criteria for recovering or recovered status, indicating that a small subset of patients have chronic suicidal ideation despite recovery.

CONCLUSION

Bipolar disorder is often comorbid with other Axis I and Axis II disorders, and this comorbidity tends to worsen the course of illness and increase the number of associated problems. Comorbidity contributes to an earlier age at onset, a more severe course of illness, more re-

current depression, and a higher chance of suicidality. Specifically, the data from the first 500 participants in STEP-BD show that anxiety and ADHD comorbidity is common among patients with bipolar disorder. Although gender differences exist in the course of bipolar illness, comorbidity rates seem to be similar between genders.

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this activity.

REFERENCES

1. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry* 2001;158:420–426
2. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* 2003;64:161–174
3. Vieta E, Colom F, Corbella B, et al. Clinical correlates of psychiatric comorbidity in bipolar I patients. *Bipolar Disord* 2001;3:253–258
4. Vieta E, Colom F, Martinez-Aran A, et al. Bipolar II disorder and comorbidity. *Compr Psychiatry* 2000;41:339–343
5. Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2004;161:2222–2229
6. Nierenberg AA, Miyahara S, Spencer T, et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biol Psychiatry* 2005;57:1467–1473
7. Goldberg JF. Bipolar disorder with comorbid substance abuse: diagnosis, prognosis, and treatment. *J Psychiatr Pract* 2001;7:109–122
8. Strakowski S, Tohen M, Stoll A, et al. Comorbidity in mania at first hospitalization. *Am J Psychiatry* 1992;149:554–559
9. Keck PE Jr, McElroy SL, Strakowski SM, et al. 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. *Am J Psychiatry* 1998;155:646–652
10. Chengappa K, Levine J, Gershon S, et al. Lifetime prevalence of substance abuse or alcohol abuse and dependence among subjects with bipolar I and bipolar II disorders in a voluntary registry. *Bipolar Disord* 2000;2:191–195
11. Brady K, Casto S, Lydiard R, et al. Substance abuse in an inpatient psychiatric sample. *Am J Drug Alcohol Abuse* 1991;17:389–397
12. Tohen M, Zarate C Jr. Bipolar disorder and comorbid substance use disorder. In: Goldberg J, Harrow M, eds. *Bipolar Disorder: Clinical Course and Outcome*. 1st ed. Washington, DC: American Psychiatric Publishing, Inc; 1999:171–184
13. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990;264:2511–2518
14. Goodwin FK, Jamison KR. *Manic-Depressive Illness*. New York, NY: Oxford University Press; 1990
15. Baldassano C, Marangell L, Gyulai L, et al. Gender differences in bipolar disorder: retrospective data from the first 500 STEP-BD participants. *Bipolar Disord* 2005;7:465–470
16. Frye M, Altshuler L, McElroy S, et al. Gender differences in prevalence, risk, and clinical correlates of alcoholism comorbidity in bipolar disorder. *Am J Psychiatry* 2003;160:883–889
17. Chessick C, Allen M, Goldberg J. Bipolar disorder with/without suicidal ideation: data from the first 500 STEP-BD participants. Presented at the 36th Annual Meeting of the American Association of Suicidology; April 2003; Santa Fe, NM