Clinical Outcomes Associated With Comorbid Posttraumatic Stress Disorder Among Patients With Bipolar Disorder

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ABSTRACT

Objective: To assess clinical outcomes associated with the presence of a lifetime history of comorbid posttraumatic stress disorder in subjects with bipolar disorder.

Methods: This cross-sectional study of 284 subjects with bipolar disorder (*DSM-IV*) assessed the association between lifetime comorbid posttraumatic stress disorder (*DSM-IV*) and clinical characteristics. Participants were included from January 2006 to June 2009. We assessed age at onset, number of mood episodes, presence of rapid cycling, first drug use, suicide attempts, hospitalizations, functional impairment, and quality of life. Diagnostic, clinical, and functional assessments were carried out using the Structured Clinical Interview for *DSM-IV* Axis I Disorders, patient edition (SCID-I/P), the Functioning Assessment Short Test, and the World Health Organization Quality of Life scale. The number of manic episodes as assessed by SCID-I/P was the primary outcome.

Results: The prevalence of lifetime comorbid posttraumatic stress disorder was 19.7% (56 subjects). Subjects with bipolar disorder and posttraumatic stress disorder had an accelerated course of illness, with a lower age at onset of manic/hypomanic episodes ($P = .009$) and earlier initiation of illicit drug use ($P = .008$). In addition, they were more likely to be younger when they received the diagnosis of bipolar disorder ($P = .036$) and had a higher number of manic/hypomanic episodes ($P = .01$). Quality of life was worse in all domains among subjects who presented the comorbidity, and rates of functional impairment were higher.

Conclusions: Comorbid posttraumatic stress disorder was associated with increased morbidity and accelerated illness progression among subjects with bipolar disorder.

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Lifetime prevalence of bipolar disorder is 2.1% worldwide, with subthreshold forms affecting another 2.4%.[1] Posttraumatic stress disorder (PTSD) has an estimated lifetime prevalence of 7.6% in the general population.[2] Both disorders have been independently associated with missed workdays,[3,4] comorbid cardiovascular[5,6] and endocrine diseases,[6,7] suicide attempts,[8,9] and structural brain changes in magnetic resonance imaging.[10–12] In a sample of adult primary care patients, those with bipolar disorder were 2.9 times as likely to screen positive for current PTSD compared with patients without bipolar disorder.[13] Moreover, the National Comorbidity Survey Replication has shown that the lifetime prevalence of PTSD among patients with bipolar disorder is 24%.[1] When compared to patients with major depressive disorder (MDD) or schizophrenia, patients with bipolar disorder have a greater risk for PTSD.[14–16]

Despite the frequent co-occurrence of PTSD and bipolar disorder, the clinical relevance of PTSD comorbidity among patients with bipolar disorder is largely unknown.[17] PTSD is often unrecognized in clinical practice among patients with bipolar disorder.[18] Cross-sectional studies[15,19] have shown that comorbid PTSD is associated with worse quality of life and higher rates of suicide attempts among patients with bipolar disorder. In addition, it has been proposed that traumatic stress and number of mood episodes may show sensitization to themselves and cross-sensitization to one another, leading to residual vulnerabilities to further occurrences of mood episodes, faster illness stage progression, and early drug misuse.[20] Therefore, one could hypothesize that the stress-induced behavioral sensitization related to PTSD may be associated with a more pernicious course of bipolar disorder illness.

Given the high prevalence of comorbid PTSD among patients with bipolar disorder and the dearth of studies in this field, we set forth to study correlates of accelerated illness progression such as (1) age at onset of first manic/hypomanic and depressive episodes, age at first drug use, and age at first bipolar disorder diagnosis[21]; (2) number of manic/hypomanic and depressive episodes, lifetime hospitalization, rapid cycling, suicide attempts, and drug abuse[22]; and (3) quality of life and functional impairment.

METHODS

We performed a cross-sectional study to assess subjects who had bipolar disorder with a lifetime PTSD diagnosis versus those who had bipolar disorder without PTSD. The study was approved by the Institutional Review Boards of the University of Texas Health Science Center at San Antonio and the University of North Carolina at Chapel Hill. Subjects signed informed consent before any study-related procedures after a complete description of the study with ample time for questions. Participants were included from January 2006 to June 2009.

Clinical Points

- Comorbid PTSD is associated with increased morbidity among subjects with bipolar disorder, including more manic/hypomanic episodes, worse quality of life, and more functional impairment.
- Comorbid PTSD is associated with a lower age at onset of manic/hypomanic episodes and first drug use in individuals with bipolar disorder.
- Psychosocial interventions and prazosin may offer an important alternative to antidepressants in bipolar subjects with comorbid PTSD.

Participants

Subjects were recruited from the community and psychiatric clinics through flyers and radio and newspaper advertisements. Inclusion criteria were bipolar disorder types I, II, or not otherwise specified (NOS) according to *DSM-IV* and age between 18 and 65 years. Exclusion criteria were head trauma with residual effects, neurologic disorder, and uncontrolled major medical conditions.

Assessments

Subjects were evaluated through a sociodemographic history form to assess age, gender, years of education, and occupational status. Axis I diagnoses and clinical characteristics were assessed with the Structured Clinical Interview for *DSM-IV* Axis I Disorders, patient edition (SCID-I/P),[23] which was administered by fully trained staff. In addition, we used SCID-I/P to assess psychiatric history, current mood status, number of mood episodes (depressive and manic/hypomanic), age at onset of first episode (depressive and manic/hypomanic), age at first drug use, age at first PTSD symptoms, and age first diagnosed with bipolar disorder (when subject received the first diagnosis by a physician). Current dimensional mood symptoms were assessed with the Hamilton Depression Rating Scale (HDRS),[24] Young Mania Rating Scale (YMRS),[25] and Hamilton Anxiety Rating Scale (HARS).[26] Data from all instruments were collected regardless of treatment or mood status.

The Functioning Assessment Short Test (FAST) was performed to assess functional impairment.[27] The FAST is a 24-item scale that assesses 6 functional domains: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. Higher scores indicate higher degrees of functional impairment. This scale has been widely used in order to assess functional impairment among subjects with bipolar disorder.[28] We also performed the World Health Organization Quality of Life, short version (WHOQOL-BREF), to assess quality of life. This instrument was developed by the World Health Organization and validated in several studies.[29] Apart from the first 2 items of general nature, the remaining 24 items of the WHOQOL-BREF comprise 4 domains: physical health, psychological health, social relationships, and environment. Higher scores show a higher quality of life.

Table 1. Demographic and Clinical Characteristics of Patients With Bipolar Disorder With and Without Lifetime PTSD

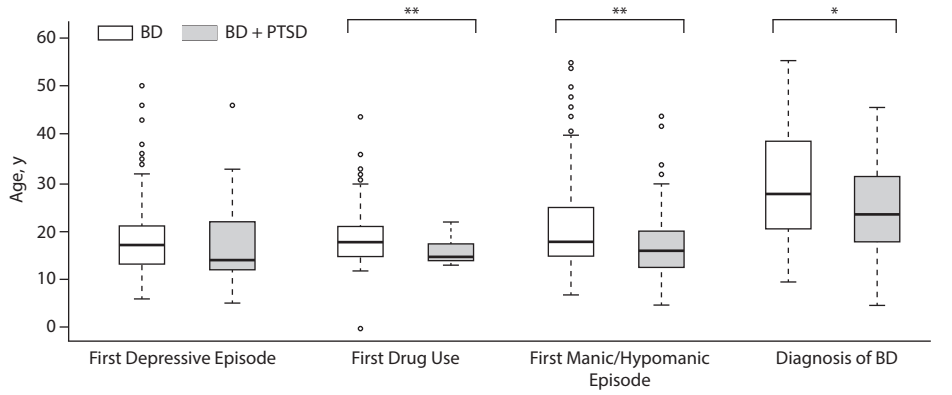
Characteristic	BD (n = 228)	BD + PTSD (n = 56)	*P* Value
Age, y[a]	37.00 ± 12.52	35.39 ± 10.40	.373
Years of education[a]	14.15 ± 2.98	13.60 ± 4.03	.357
Manic symptoms[b]	4 (1/8)	7 (3/11)	.002
Depressive symptoms[c]	11 (5/18)	18 (12/21)	< .001
Anxiety symptoms[d]	11 (5/17)	15 (8/21)	.012
Gender[e]			
Male	35.5% (81)	26.8% (15)	.280
Female	64.5% (147)	73.2% (41)	
Currently employed[e]	42.1% (96)	41.1% (23)	1.00
Diagnosis of BD[e]			
BD I	64.5% (147)	75.0% (42)	.273
BD II	27.6% (63)	21.4% (12)	
BD not otherwise specified	7.9% (18)	3.6% (2)	
Rapid cycling[e,f]	40.2% (72)	48.9% (22)	.377
Prevalence of prior mixed episodes[e,f]	14.2% (24)	26.8% (11)	.052
Comorbid medical illness[e]	15.8% (36)	14.3% (8)	.982
Comorbid substance abuse or dependence[e]	37.7% (86)	44.6% (25)	.425
Lifetime suicide attempts[e,f]	34.5% (60)	42.1% (16)	.483
Lifetime hospitalization[e]	43.4% (99)	48.2% (27)	.563
Lifetime psychotic symptoms[e]	26.3% (60)	30.4% (17)	.572
Current medication[e]			
Antidepressants	17.5% (40)	12.5% (7)	.426
Lithium	6.1% (14)	1.8% (1)	.209
Anticonvulsants	21.5% (49)	14.3% (8)	.279
Atypical antipsychotics	13.2% (30)	12.5% (7)	.985
Typical antipsychotics	0.9% (2)	0% (0)	.491
Benzodiazepines	16.2% (37)	19.6% (11)	.449
Comorbid anxiety disorder[e]			
GAD	12.7% (29)	17.9% (10)	.317
OCD	8.8% (20)	10.7% (6)	.652
Social phobia	12.7% (29)	8.9% (5)	.243
Panic disorder	19.7% (45)	26.8% (15)	.247

[a]Mean and standard deviation; *P* value according to Student *t* test.
[b]YMRS median (25th/75th quartiles) score; *P* value according to Mann-Whitney *U* test.
[c]HDRS median (25th/75th quartiles) score; *P* value according to Mann-Whitney *U* test.
[d]HARS median (25th/75th quartiles) score; *P* value according to Mann-Whitney *U* test.
[e]Relative (%) and absolute (n) frequencies; *P* value according to χ^2 test.
[f]Presence of missing data.
Abbreviations: BD = bipolar disorder, GAD = generalized anxiety disorder, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, YMRS = Young Mania Rating Scale.

Statistical Analyses

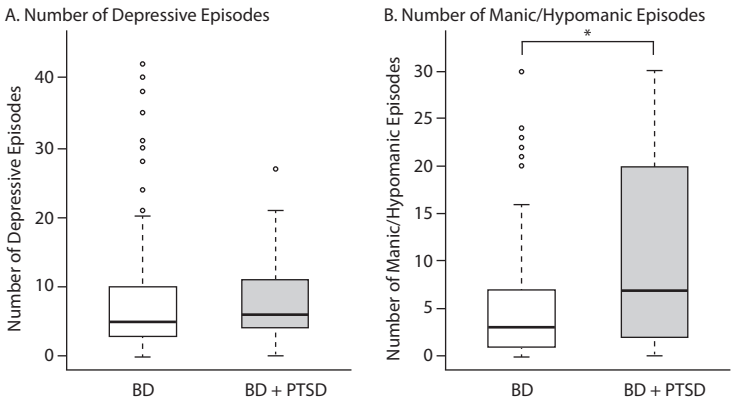
Statistical analyses were conducted using IBM SPSS software (version 21). Descriptive analyses were reported as means (standard deviations), medians (interquartile range), or absolute and relative frequencies. We used χ^2, Student *t*, or Mann-Whitney *U* tests to analyze demographic and clinical variables. We divided participants into 2 groups: subjects with bipolar disorder and lifetime comorbid PTSD diagnosis and subjects with bipolar disorder without PTSD across lifespan. Number of mood episodes, functional impairment (FAST), age at first mood episode, age first diagnosed with bipolar disorder, and age at first drug use were analyzed with the Mann-Whitney *U* test since it has nonparametric distribution. Linear regression adjusted for current mood and anxiety symptoms was performed to verify the effect of comorbid PTSD in functional impairment and quality of life. *P* values < .05 were considered significant. Number

Figure 1. Age at Onset of Mood Episodes, Drug Use, and Diagnosis of Bipolar Disorder Among Patients With and Without Lifetime PTSD Comorbidity[a]



[a]The box represents minimum, first quartile, median (heavy line), third quartile, and maximum. Any data not included between the whiskers were plotted as an outlier with a dot.
*P < .05. **P < .01.
Abbreviations: BD = bipolar disorder, PTSD = posttraumatic stress disorder.

Figure 2. Number of Depressive and Manic/Hypomanic Episodes in Bipolar Disorder Patients With and Without Lifetime PTSD[a]



[a]The box represents minimum, first quartile, median (heavy line), third quartile, and maximum. Any data not included between the whiskers were plotted as an outlier with a dot.
*P < .05; adjusted for age at onset of first manic/hypomanic episode.
Abbreviations: BD = bipolar disorder, PTSD = posttraumatic stress disorder.

of manic/hypomanic episodes was adjusted for age at onset of manic/hypomanic episodes.

RESULTS

A total of 284 subjects with bipolar disorder were included in all mood states. Among them, 80 (28.2%) were euthymic, 147 (51.8%) were depressed, 33 (11.6%) were manic/hypomanic, and 24 (8.4%) were mixed. Moreover, 42% of the recruited patients were receiving outpatient psychiatric care, whereas 58% were not. Fifty-six subjects (19.7%) showed lifetime comorbid PTSD diagnosis, and 25 subjects (8.8%) had current PTSD symptoms. PTSD occurred prior to bipolar disorder in 68% of subjects with bipolar disorder and PTSD. Prevalence of PTSD comorbidity among subjects with bipolar disorder was 22.2% in bipolar disorder type I, 16.0% in bipolar disorder type II, and 10.0% in bipolar disorder NOS. However, there was no difference among groups in prevalence (P = .273). Table 1 shows demographics and clinical characteristics.

The median and interquartile range of age at onset of PTSD symptoms were 14 (11–23) years among subjects with lifetime comorbid PTSD diagnosis. Figure 1 shows that subjects with bipolar disorder and PTSD (BD + PTSD) had an earlier onset of manic/hypomanic episodes (BD + PTSD: 16 [13–20] vs BD: 18 [15–25] years; P = .009) and first drug use (15 [14–18] vs 18 [15–21] years; P = .008). Moreover, subjects with BD + PTSD were younger when first diagnosed with bipolar disorder (24 [18–32] vs 28 [21–39] years; P = .036). The onset of depressive episodes (P = .548) was not significantly different between groups.

Subjects with BD + PTSD reported higher numbers of manic/hypomanic episodes than subjects with bipolar disorder without PTSD (7 [2–20] vs 3 [1–7] episodes; P = .012) (Figure 2B), even when adjusted for age at onset of manic/hypomanic episodes (P = .016). However, number of depressive episodes was not significantly higher in subjects with BD + PTSD (6 [4–12] vs 5 [3–10] episodes; P = .278) (Figure 2A).

Subjects with BD + PTSD showed higher functional impairment (46 [33–50] vs 24 [16–38]; P = .022) (Figure 3). Quality of life (Figure 4) was poorer in subjects with BD + PTSD regarding physical health (37.3 ± 16.4 vs 49.1 ± 14.1; P = .005), psychological health (40.3 ± 13.8 vs 52.3 ± 14.3; P = .004), social relationships (37.9 ± 23.1 vs 53.2 ± 26.4; P = .039), and environment (48.2 ± 20.4 vs 70.9 ± 15.1; P = .001). Subjects with BD + PTSD showed higher scores of depressive (P < .001), manic (P = .002), and anxiety (P = .012) symptoms when compared to bipolar subjects without PTSD. The difference among groups in FAST and

WHOQOL-BREF scores remained statistically significant after adjustment for severity of depressive, manic, and anxiety symptoms, except for social relationships (Figure 4).

DISCUSSION

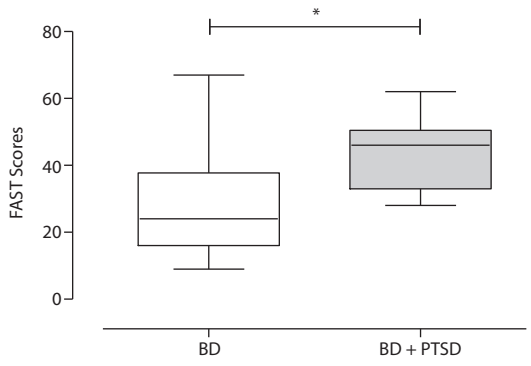
The present study showed that subjects who have bipolar disorder comorbid with PTSD had a lower age at onset of manic/hypomanic episodes and first drug use and were also more likely to be younger when they received the diagnosis of bipolar disorder. This group also shows more manic/hypomanic episodes, worse quality of life, and more functional impairment. Our study suggests that comorbid PTSD is associated with accelerated illness progression and increased morbidity in bipolar disorder.[30] The lifetime prevalence of PTSD among subjects with bipolar disorder was 19.7% in our sample. This rate is similar to that found in the Systematic Treatment Enhancement Program for Bipolar Disorder (18.8%).[31]

The association of comorbid PTSD among subjects with bipolar disorder regarding the clinical variables assessed (age at onset of manic episode, first drug use, and first diagnosis of bipolar disorder and number of manic/hypomanic episodes) has not been reported so far. This finding is in line with the notion that the stress sensitization related to PTSD leaves residual vulnerabilities to further occurrences of mood episodes and accelerated illness progression.[20,32] A cohort study has shown similar results among 651 patients with bipolar disorder, but studying another kind of stress.[33,34] Patients with early childhood trauma also had earlier onset of bipolar illness, a greater number of subsequent manic episodes, faster cycling pattern, more suicide attempts, and higher incidence of substance abuse.[33,34] Although the age at onset of PTSD symptoms in our sample precedes the age at first bipolar disorder diagnosis, we cannot exclude the possibility that number of manic/hypomanic episodes leads to increased risk of developing PTSD since this is a cross-sectional study.

Our study also showed that PTSD comorbidity among subjects with bipolar disorder was associated with worse quality of life and functional impairment. A previous study[19] of 405 patients with bipolar disorder found worse quality of life in 3 domains of the WHOQOL-BREF (psychological health, social relationships, and environment) in the comorbid PTSD group. No study so far has reported the association of PTSD comorbidity with functioning impairment among subjects with bipolar disorder. Functional impairment is a key clinical feature in PTSD and bipolar disorder.[35,36] A previous study[37] of 3,345 patients with bipolar disorder has shown that multiple mood episodes were associated with worse functioning and lower quality of life. Even young subjects with bipolar disorder have shown functional impairment, which gets worse with illness progression.[36,38,39] It was proposed that PTSD stress and manic episodes may have sensitization to themselves and cross-sensitization to one another contributing to a pernicious course among bipolar disorder patients with even more functional impairment.[30,32]

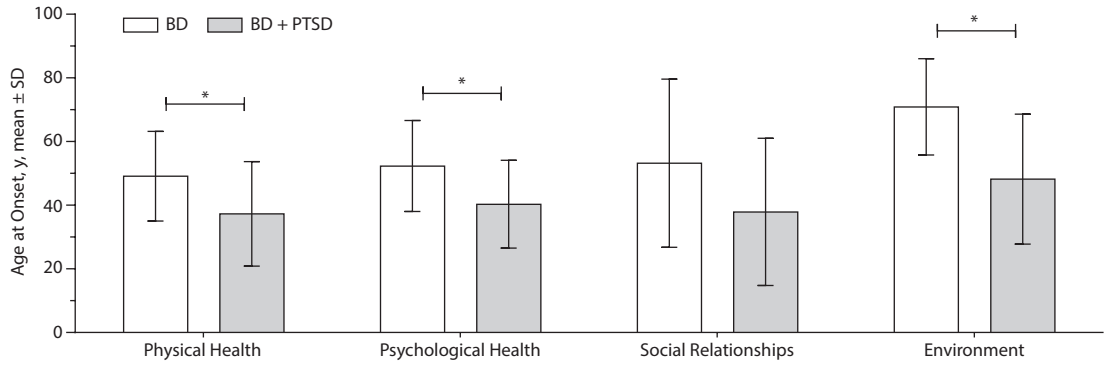
PTSD and bipolar disorder share some biological underpinnings, which may explain the interaction of both disorders contributing to accelerated illness progression among patients with bipolar disorder.[30,40] Serum concentrations of brain-derived neurotrophic factor

Figure 3. Functional Impairment in Bipolar Disorder Patients With and Without Lifetime PTSD[a]



[a]The box represents minimum, first quartile, median (heavy line), third quartile, and maximum.
*$P < .05$; adjusted for severity of depressive, manic, and anxiety symptoms.
Abbreviations: BD = bipolar disorder, FAST = Functioning Assessment Short Test, PTSD = posttraumatic stress disorder.

Figure 4. Quality of Life in Bipolar Disorder Patients With and Without Lifetime PTSD



*$P < .05$; adjusted for current severity of depressive, manic, and anxiety symptoms.
Abbreviations: BD = bipolar disorder, PTSD = posttraumatic stress disorder.

(BDNF) are decreased in drug-free bipolar disorder patients during manic episodes,[41] as well as in drug-naive patients with PTSD.[42] Also, exposure to traumatic events may induce epigenetic modification leading to further reductions of BDNF.[43,44] Moreover, levels of tumor necrosis factor-α (TNF-α) and soluble tumor necrosis factor receptor type 1 are elevated in bipolar disorder during manic episodes.[45] In addition, increased levels of TNF-α were reported in patients with PTSD.[46,47] Both decreased BDNF levels and increased TNF-α levels are associated with a more severe course of bipolar disorder.[48,49]

Considering all the findings indicating an association of comorbid PTSD and increased morbidity among subjects with bipolar disorder, an important clinical question emerges regarding current treatment practices. Antidepressants are the mainstay in the treatment of patients with PTSD. However, among patients with bipolar disorder, the clinical usefulness of antidepressants seems to be restricted to some cases of the acute treatment of bipolar depression.[50] Psychosocial interventions that have been shown to improve both PTSD and bipolar disorder may offer an important alternative in this subset of patients. Also, prazosin is another useful alternative in the treatment of individuals with PTSD and bipolar disorder. Prazosin was effective for trauma nightmares, sleep quality, functioning, and hyperarousal symptom cluster in patients with PTSD.[51]

It should be mentioned in the present cross-sectional study that reverse causality could not be discarded. Whether PTSD predisposes individuals with bipolar disorder to a worse course, or whether the characteristics of the severe bipolar disorder itself determine PTSD onset remains unclear. Recall bias and the influence of current disorder may interfere in our findings. Specifically, our reliance on retrospective self-report for lifetime disorders and severity of illness in this cross-sectional assessment does not protect from the possible bias that patients with greater severity of illness may have been more likely to acknowledge a history of PTSD in a structured interview. Also, we do not know the extent to which comorbid PTSD motivates subjects to participate in research or seek care. However, the inclusion of patients at all levels of symptom severity, treatment, and phase of illness allows for a broad generalizability. Future longitudinal studies including prospective follow-up will be needed to confirm the present findings and provide further information regarding the phenomenological changes in the course of bipolar disorder with PTSD.

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Drug names: lithium (Lithobid and others), prazosin (Minipress and others).

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