Clinical Outcomes in Children and Adolescents With Bipolar Disorder and Substance Use Disorder Comorbidity

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ABSTRACT

Objective: To assess the global functioning and clinical outcomes of children and adolescents with bipolar disorder, children and adolescents with bipolar disorder and substance use disorder (SUD) comorbidity and healthy controls.

Methods: This study had a cross-sectional design. Participants were children and adolescents aged between 6 and 17 years, and data were collected between 2003 and 2015. Psychiatric diagnosis was established according to *DSM-IV* criteria using the Kiddie-SADS-Present and Lifetime Version or the Mini-International Neuropsychiatric Interview for Children and Adolescents. Global functioning was assessed using the Children's Global Assessment Scale. Depressive symptoms were assessed using the Children's Depression Rating Scale. Manic symptoms were measured using the Young Mania Rating Scale, and the severity of anxious symptoms was assessed using the Screen for Child Anxiety Related Disorders.

Results: The sample included 187 children and adolescents with bipolar disorder, 29 with BD and SUD comorbidity, and 115 healthy controls. Children and adolescents with BD and SUD comorbidity presented later onset of mood disorder ($P < .001$); higher rates of lifetime history of suicide attempt ($P < .001$), lifetime history of psychosis (trend toward significance: $P = .076$), and lifetime hospitalization ($P < .001$); and higher severity of depressive symptoms (trend toward significance: $P = .080$) as compared to those with BD without SUD comorbidity. In addition, both diagnosis groups presented higher rates of functional impairment when compared to controls ($P < .001$). Moreover, BD and SUD comorbidity presented higher functional impairment, as compared to BD without SUD comorbidity ($P = .020$).

Conclusions: Children and adolescents with bipolar disorder and substance use disorder comorbidity present a worse clinical course than those with bipolar disorder but without substance use disorder comorbidity.

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The prevalence of bipolar disorder is 1.8% in pediatric samples.[1] In addition, the lifetime prevalence of bipolar disorder among adolescents aged 13–17 years old is 3.0%.[2] Pediatric bipolar disorder is frequently accompanied by other psychiatric disorders, and studies estimate that the prevalence of substance use disorder (SUD) ranges from 16% to 39% in adolescents with bipolar disorder.[3]

Duffy et al[4] found a prevalence of 23.7% for lifetime SUD in a study that assessed the relationship between SUD and the early clinical course of bipolar disorder in offspring of parents with bipolar disorder. In addition, offspring with SUD had a significantly higher probability of meeting criteria for a lifetime major mood episode (major depression, hypomania, or mania), a higher risk of having experienced psychotic symptoms, and greater functional impairment compared to those offspring without SUD.[4] A recent review[3] verified also that youth with bipolar disorder and SUD comorbidity present a worse clinical course and prognosis. Comorbid SUD has been associated with mood recurrence, medication nonadherence, suicidality, legal problems, and adolescent pregnancy.[3]

Post and Kalivas[5] postulated that the cross-sensitization among stressors, episodes, and substance misuse contributes to illness progression. Moreover, functional impairment has also been considered as a marker of clinical staging of bipolar disorder in adults.[6] However, few studies have investigated the impact of substance use disorder comorbidity on clinical outcomes of bipolar disorder in child and adolescent samples. It is important to examine factors associated with substance use disorder in youth with bipolar disorder because early identification and management may improve the prognosis of bipolar disorder.

Thus, the aim of this study was to assess the global functioning and clinical outcomes of children and adolescents with bipolar disorder without substance use disorder comorbidity, those with bipolar disorder and substance use disorder comorbidity, and healthy controls.

METHODS

For this cross-sectional study, participants were recruited from outpatient clinics at the University of Texas Health Science Center at San Antonio (UTHSCSA), at the University of North Carolina at Chapel Hill (UNC), and at the University of Texas Health Science Center at Houston (UTHSCH). The recruitment strategies were the same between the 3 clinical sites. The subjects were recruited

Clinical Points

- Youth with bipolar disorder plus substance use disorder comorbidity present a worse clinical course of illness.
- Functioning is more impaired in youth with bipolar disorder plus substance use disorder as compared to those who have bipolar disorder without this comorbidity.

through newspaper and television advertisements and flyers posted in the communities where the study was carried out (UTHSCSA, UNC, and UTHSCH). The data were collected between 2003 and 2015. The study protocol was approved by the local institutional review boards, and informed consent was obtained from all the participants' legal guardians.

Participants were children and adolescents aged between 6 and 17 years. Socioeconomic status was assessed using the Hollingshead Four-Factor Index of Socioeconomic Status.[7] Psychiatric diagnoses, such as bipolar disorder and substance use disorder (SUD), were established based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria, using the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL)[8] interview or the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).[9] In addition, the clinical interview was used to assess the current mood state of the patients. Healthy controls were children and adolescents with no Axis I diagnosis, no history of substance use, and no current medical problems. When healthy controls presented history of any mood disorder in first-degree relatives, they were excluded.

Clinical characteristics were also collected, such as history of mental disorders in first-degree relatives, age at onset of mood disorders, lifetime history of psychosis, lifetime history of suicide attempt, lifetime hospitalization, and current use of psychopharmacologic medication. Depressive symptoms were assessed using the Children's Depression Rating Scale (CDRS).[10] This instrument comprises 17 items and was developed for pediatric patients (above 6 years). Manic symptoms were measured using Young Mania Rating Scale (YMRS).[11] Severity of symptoms is based on the ratings of 11 items. The Screen for Child Anxiety Related Disorders (SCARED)[12] scale includes 41 items approaching different domains of anxiety and provides an important screening and follow-up tool for clinical and research assessments. General functioning was assessed using the Children's Global Assessment Scale (CGAS).[13] This is a 100-point scale on which higher scores mean better functioning.

Statistical analyses were performed using SPSS 21.0 (IBM). Subjects were grouped according to diagnoses: bipolar disorder (BD) with substance use disorder (SUD) was coded as BD + SUD, BD without SUD comorbidity was coded as BD, and healthy children and adolescents, as control group. One-way analysis of variance followed by Bonferroni post hoc test, χ^2 test, and Mann-Whitney *U* test were conducted to assess demographic and clinical characteristics across groups. Linear regression was used to adjust for possible confounders. Potential confounders were considered in statistical analysis when associated to the dependent and independent variables ($P < .20$).

RESULTS

The sample included 187 children and adolescents with BD (mean ± SD = 12.58 ± 2.98 years, 102 males), 29 with BD + SUD (mean ± SD = 15.77 ± 1.12 years, 14 males), and 115 control group subjects (mean ± SD 12.54 ± 3.00 years, 62 males). The sociodemographic characteristics of the sample are described in Table 1.

The majority of the subjects with BD + SUD had used cannabis (n = 15, 51.7%), followed by multiple substances (n = 12, 41.4%), alcohol (n = 1, 3.4%), and other substance (n = 1, 3.4%). The mean age at onset of SUD was 12.39 ± 2.39 years. Table 2 presents the clinical characteristics between bipolar disorder without SUD comorbidity and bipolar disorder with SUD comorbidity. Of note, children and adolescents with BD and SUD comorbidity presented significantly later age at onset of mood disorder ($P < .001$); higher rates of lifetime history of suicide attempt ($P < .001$), lifetime hospitalization ($P < .001$), and lifetime history of psychosis (trend toward significance: $P = .076$); and higher severity of depressive symptoms (trend toward significance: $P = .080$).

The mean global functioning among the groups was 92.25 ± 7.05 for controls, 52.47 ± 10.55 for BD, and 47.38 ± 8.77 for BD + SUD. Both diagnosis groups presented higher rates of functional impairment when compared to the control group ($P < .001$). In addition, BD + SUD presented higher functional impairment compared to BD without SUD comorbidity ($P = .020$) (Figure 1). In a linear regression model, we found a difference in functioning across the groups even after statistical adjustment for ethnicity, economic status, and current mood state (B = −23.244 [95% CI, −25.755 to −20.732], $P < .001$).

DISCUSSION

This study showed that youth with bipolar disorder and SUD demonstrate a worse clinical course than bipolar disorder without SUD. In addition, both groups of patients with bipolar disorder (with and without SUD) presented more impairment in functioning as compared to healthy controls. Moreover, bipolar disorder with SUD presented more functional impairment than bipolar disorder without SUD.

A study that assessed the association between medical and psychiatric comorbidities, clinical characteristics, and course of illness in pediatric bipolar disorder showed that neuropsychiatric (attention-deficit/hyperactivity disorder, substance abuse, and epilepsy) and medical (obesity, asthma, cardiovascular disease) conditions temporally precede the diagnosis of early-onset bipolar disorder, and specifically endocrine disorders and substance abuse were associated with recurrent depressive episodes.[14] In addition, another

Table 1. Sociodemographic Characteristics Among the Diagnosis Groups and Healthy Controls

Characteristic	Controls (n = 115)	BD (n = 187)	BD + SUD (n = 29)	*P* Value
Gender, n (%)				
Male	62 (53.9)	102 (54.5)	14 (48.3)	.819
Female	53 (46.1)	85 (45.5)	15 (51.7)	
Age, mean ± SD, y	12.54 ± 3.00	12.58 ± 2.98	15.77 ± 1.12	< .001
Ethnicity, n (%)				
Hispanic or Latino	52 (45.2)	46 (24.6)	12 (41.4)	.005
Non-Hispanic or non-Latino	62 (53.9)	138 (73.8)	17 (58.6)	
Unknown	1 (0.9)	3 (1.6)	…	
Years of education, mean ± SD	6.54 ± 3.10	6.48 ± 2.95	9.28 ± 1.36	< .001
Hollingshead socioeconomic status, mean ± SD	49.76 ± 11.96	36.65 ± 16.11	34.17 ± 18.99	< .001

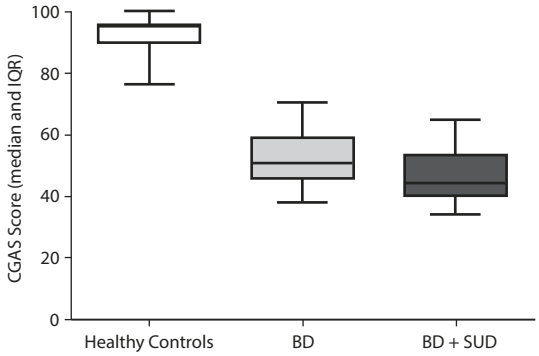
Abbreviations: BD = bipolar disorder, SUD = substance use disorder.

Table 2. Clinical Characteristics Between Bipolar Disorder (BD) and Bipolar Disorder With Substance Use Disorder Comorbidity (BD + SUD)

Characteristic	BD (n = 187)	BD + SUD (n = 29)	*P* Value
Subtype of BD, n (%)			
BD I	86 (46.0)	14 (48.3)	.492
BD II	28 (15.0)	2 (6.9)	
BD NOS	73 (39.0)	13 (44.8)	
History of mental disorder in first-degree relatives, n (%)	160 (86.5)	23 (79.3)	.461
Age at onset of mood disorder, mean ± SD, y	9.25 ± 3.25	12.83 ± 2.70	< .001
Lifetime history of psychosis, n (%)	70 (40.7)	17 (60.7)	.076
Lifetime history of suicide attempt, n (%)	29 (18.7)	18 (66.7)	< .001
Lifetime hospitalization, n (%)	75 (40.3)	24 (82.8)	< .001
Current psychiatric medication, n (%)	126 (68.9)	24 (82.8)	.190
Current mood state, n (%)			
Euthymic	57 (36.3)	10 (37.0)	.196
Depressive episode	48 (30.6)	13 (48.1)	
Hypomanic/manic episode	27 (17.2)	2 (7.4)	
Mixed episode	25 (15.9)	2 (7.4)	
CDRS score, mean ± SD	34.65 ± 12.60	40.43 ± 16.15	.080
YMRS score, median (interquartile range)	9.00 (4.00–14.00)	6.00 (2.00–12.00)	.215
SCARED score, median (interquartile range)	29.00 (19.50–41.00)	27.00 (6.50–44.50)	.535

Abbreviations: CDRS = Children's Depression Rating Scale, NOS = not otherwise specified, SCARED = Screen for Child Anxiety Related Disorders, YMRS = Young Mania Rating Scale.

Figure 1. Global Functioning Across the Groups[a]



[a]A significant difference in CGAS score was found when subjects with BD and BD + SUD were compared to controls ($P < .001$) and when subjects with BD and BD + SUD were compared ($P = .020$). Differences were assessed using Bonferroni post hoc test.
Abbreviations: BD = bipolar disorder, CGAS = Children's Global Assessment Scale, IQR = interquartile range, SUD = substance use disorder.

study showed that offspring with SUD had a significantly higher probability of meeting criteria for a lifetime major mood episode, a higher risk of having experienced psychotic symptoms, and higher functional impairment compared to those offspring without SUD.[4] These findings were similar to our results; we also found higher rates of lifetime history of suicide attempt, lifetime hospitalization, and trends toward higher rates of psychotic symptoms and higher severity of depressive symptoms in youth with bipolar disorder and SUD comorbidity than in youth with only bipolar disorder. These results demonstrate a worse clinical course of illness in subjects with substance use disorder comorbidity.

Global functioning is an important clinical outcome to be investigated in bipolar disorder. In adult samples, functional impairment has been considered a marker of clinical staging in bipolar disorder.[6,15,16] A study comparing patients with major depressive disorder (MDD), patients with bipolar disorder, and healthy controls found that patients with bipolar disorder presented more functional impairment than those with MDD; in addition, even during remission periods, both subjects with bipolar disorder and those with MDD presented more functional impairment compared to healthy controls.[17] In a pediatric sample, a study showed that children with some psychopathology were significantly more functionally impaired than those without psychopathology.[18] Importantly, that study verified that children who were functionally impaired were observed to have more developmental delays.[18] However, there have been no studies investigating functional impairment in children/adolescents with bipolar disorder and substance use disorder comorbidity. In our sample, bipolar disorder (with and without SUD) presented more impairment in functioning as compared to healthy controls. Moreover, bipolar disorder with SUD presented more functional impairment than bipolar disorder without SUD.

Our study showed a worse clinical outcome in subjects with bipolar disorder and SUD comorbidity. This study was conducted with a sample of children and adolescents in light of the dearth of studies in this population and the fact that it is important to investigate impairments at the onset of illness, enabling the design of intervention strategies. However, this study does have a limitation, as it is a cross-sectional study and we cannot investigate the causal relationship between comorbidity and clinical outcomes. It has recently been discussed that mood disorders are risk factors to the onset of SUD.[19] In this sense, early identification and prevention of

SUD are important for the reduction of the damaging impact of SUD on the course of bipolar disorder. A recent study has assessed the effectiveness of family-focused treatment for adolescents with bipolar disorder and comorbid substance use disorders, as an adjunct to pharmacologic treatment, and it was verified that after the treatment, subjects with bipolar disorder and SUD comorbidity demonstrated significant improvements in depressive symptoms, manic symptoms, and global functioning.[20] It is important to highlight that these are preliminary results from a pilot study including only 10 patients (only 6 completed the treatment) and do not include a control group. Thus, more studies are needed to assess the effectiveness of the psychosocial interventions for youth with bipolar disorder and SUD comorbidity.

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