

ORIGINAL ARTICLE

Psychotic and affective symptoms of early-onset bipolar disorder: an observational study of patients in first manic episode

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Objective: Presence of psychotic symptoms seems to be a commonplace in early-onset bipolar disorder (BD). However, few studies have examined their occurrence in adolescent-onset BD. We sought to investigate the frequency of affective and psychotic symptoms observed during the first manic episode in adolescents.

Methods: Forty-nine adolescents with bipolar I disorder (DSM-IV criteria) were admitted to a psychiatric hospital during their first acute manic episode. Assessment for current psychiatric diagnosis was performed by direct clinical interview and the DSM-IV version of the Diagnostic Interview for Children and Adolescents (DICA).

Results: Teenage inpatients with BD consistently exhibited typical manic features, such as euphoria, grandiosity, and psychomotor agitation. In addition, disorganization and psychotic symptoms were present in 82 and 55% of the total sample, respectively. There was no significant difference in symptoms between early- and late-adolescent subgroups. Remarkably, most patients (76%) reported previous depressive episode(s); of these, 47% had prominent psychotic features in the prior depressive period.

Conclusion: These findings suggest that disorganization and psychotic symptoms during the first manic episode are salient features in adolescent-onset BD, and that psychotic depression frequently may precede psychotic mania. Nevertheless, differential diagnosis with schizophrenia should be routinely ruled out in cases of early-onset first psychotic episode.

Keywords: Psychosis; bipolar disorder; adolescent; psychopathology; prodromal symptoms

Introduction

There is persistent controversy in the recent literature concerning the clinical phenomena of early-onset bipolar disorder (BD).¹⁻³ Major disagreements refer to the bipolar cycling pattern and core manic symptomatology in children and adolescents.^{4,5} Specifically, the presence of psychotic symptoms seems to be more frequent in child- and adolescent-onset BD patients than in those with adult-onset BD.^{3,6-9}

Assessing psychotic symptoms in early-onset BD has been considered a critical issue in both clinical and research settings. The manifestation of BD with psychotic symptoms has been related to poorer long-term outcome, more hospitalizations, lower inter-episodic functioning, and a lower clinical recovery rate.^{7,8,10} Pediatric BD patients with psychotic symptoms may have a greater degree of neurobiological dysfunction, such as abnormalities in midline cortical structures.^{3,5,11,12}

Despite the relevance of this issue, reliable empirical investigations on psychotic symptoms observed throughout an early-onset manic episode are lacking.^{6,7,13} Psychotic syndromes have been described in youths with the diagnoses of schizophrenia, psychotic mood disorder, schizoaffective disorder, organic psychoses, and traumatic maltreatment experiences.^{6,14,15} The presence of nonspecific but key symptoms such as auditory hallucinations, grandiosity, persecutory delusion, and behavioral disorganization during early-onset BD episodes may be suggestive of schizophrenia. Likewise, negative symptoms of early-onset schizophrenia may be mistaken as depression, leading to misdiagnoses in both situations. Therefore, an accurate distinction of the array of psychotic syndromes present in childhood and adolescence remains a key challenge to practitioners, especially during the initial phase of the psychotic illness, when the clinical features are compound and symptoms often overlap.^{3,6,8,16-18}

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Child and adolescent psychiatry practitioners tended to overlook affective manifestations in patients with psychotic symptoms or to poorly investigate psychotic and disorganization symptoms in mood disorders, allowing diagnostic uncertainty between BD and schizophrenia.^{9,18} The validity and reliability of diagnosing BD and schizophrenia in children and adolescents remain a source of debate. This prevents timely diagnosis and delays treatment for both disorders.^{6,7,19,20}

The aim of the present study is to describe observational data from the occurrence of affective and psychotic symptoms among adolescent inpatients with BD-I during their first manic episode. We also investigated psychiatric phenomena that occurred before the onset of the first manic episode.

Methods

Sample

The inclusion criteria were: 1) age 12 to 18 years; 2) fulfilling the DSM-IV criterion for manic episode²¹; 3) first manic episode at index time; and 4) at least 6 months of follow-up treatment at our outpatient clinic after hospitalization. The latter criterion was used to ensure the reliability of admission diagnosis by subjecting longitudinal data to expert debate.¹⁷

The exclusion criteria were: 1) chronic medical illness; 2) history of substance abuse or dependence in the preceding 2 months (the main substances evaluated were alcohol, cannabis, stimulants, sedatives, and cocaine. Patients were excluded if they fulfilled DSM-IV criteria for substance use disorder); 3) pervasive development disorder; 4) prior history and diagnosis of schizophrenia; 5) clinical evidence of lifetime intellectual disability; and 6) inability to complete clinical interviews. In addition, we also excluded those who did not remain for the full hospitalization period recommended by the attending psychiatrist and those who did not follow up at our outpatient clinic for at least 6 months after hospitalization.

Initially, 57 adolescent inpatients with BD at first manic episode were eligible for the present study at index time. Of these, we excluded four patients (one girl and three boys) who did not complete all assessment procedures and four patients (two girls and two boys) who did not complete 6-month follow-up.

The definitive sample comprised 49 adolescents in first manic episode, hospitalized from January 1995 to December 1998 (mean inpatient period = 71 days; range, 60 to 87 days) at the inpatient unit of Serviço de Psiquiatria da Infância e Adolescência, Instituto de Psiquiatria, Universidade de São Paulo (USP), Brazil. Notably, 36 (73.5%) of the patients with BD had been followed up at our center with a previous diagnosis of major depressive disorder.

Clinical assessment

Patients' current and lifetime psychiatric diagnoses were ascertained during the first week of hospitalization, though a procedure consisting of: 1) at least one face-to-face

clinical interview with the patient and their parents separately; 2) a review of the last 24 months of the patient's clinical record, completed by the attending child psychiatrist; and 3) an interview using the DSM-IV version of the Diagnostic Interview for Children and Adolescents (DICA-IV),²² conducted by experienced child psychiatrist researchers. Functional impairment was assessed through the Children's Global Assessment Scale (CGAS).²³ A best-estimate consensus by an expert panel composed of the principal investigator and the research staff led to the definitive diagnosis, clinical feature discrimination, and outcome measurements, based on all data collected.

During the direct clinical interview, patients were allowed to talk freely, thus allowing evaluation of their behavior and speech patterns, presence of other manic symptoms, disorganization, and other psychotic symptoms.^{24,25} Information obtained during the adolescent's interview was supplemented by information gathered from the affective disorders and psychotic symptoms section of the DICA-IV. The clinical significance of all psychiatric symptoms presented during the current manic episode included the core symptoms of mania (e.g., euphoria, grandiosity, increased energy), taken into account only if they both represented an obvious change in (or clear exacerbation of preexisting) behavior during the first manic episode and caused evident functional impairment.

Disorganization and psychotic features were assessed on the basis of Scale for the Assessment of Thought, Language, and Communication (TLC), developed by Andreasen²⁵ to improve the reliability of assessment of formal thought disorder. The definition of psychotic symptoms adopted was:

- 1) Disorganized or bizarre behavior, expressed by recurring and almost constant abnormal or odd behavior. For example, during the clinical observation, the patient opened her bag and put on a swimsuit over her pants, blouse, and jacket, all the while incapable of understanding the inappropriateness of her own behavior;
- 2) Disorganized speech, expressed by pressure of speech, tangentiality, derailment, associative loosening, clanging, incoherent, or illogical speech;
- 3) Delusion, expressed by focused intention to act upon illogical beliefs, or being very bothered or distracted by such beliefs (e.g., one girl was admitted to the hospital after she tried to wear an ancient crown on display in a museum because she was fully convinced that she was Miss Brazil);
- 4) Hallucination, expressed by an intense desire to respond to voices or visions or being very bothered by voices/visions.

Statistical analysis

Descriptive statistics depicted the characteristics of the sample and its subgroups in terms of proportion for categorical variables (gender, age group, and clinical symptoms) and mean (M), standard deviation (SD), and range for continuous variables (age). The following standard parametric and nonparametric statistical tests

were used to compare between-group differences: Wilcoxon signed rank test, Kruskal-Wallis test, and Fisher's exact test. Bonferroni correction was used to protect from familywise type I error. Kaplan-Meier survival analysis was used to examine the equality distribution of the age at depressive episodes prior to the first manic episode, followed by a log rank test. All tests were two-tailed, with a significance level of 0.05. Analyses were performed in SPSS version 21.

Ethics statement

The USP ethics committee approved the present investigation, and subjects were included in the sample only after their parents or legal guardians provided written informed consent.

Results

The mean sample age was 14.3 years (SD = 2.0; range, 12 to 18 years), including 25 males and 24 females. The mean age at onset of first manic episode was significantly lower in males than females (13.9 vs. 14.9 years, $p < 0.05$). Concerning the developmental stage, there were 23 early adolescents (age < 15 years) and 26 late

adolescents (≥ 15 years).²⁶ Male patients significantly outnumbered females in the early adolescent subgroup (31 vs. 16%, $p < 0.05$), whereas females prevailed over males in the late adolescent subgroup (33 vs. 20%, $p < 0.05$). There was no evident difference in family socioeconomic status between these two developmental subgroups.

The frequency of all psychopathological symptoms during first manic episode for the total sample and stratified by the early and late adolescent groups is displayed in Figures 1 and 2. Regarding acute manic symptoms, 67% of patients presented with euphoric mood, and 45% with irritable mood. Increase in goal-directed activity was observed in 67%, and 47% manifested grandiosity. There were no significant differences between age groups concerning major manic symptoms, with exception of grandiosity, which was more common in the early adolescent subgroup (Figure 1). The global functioning of this sample was severely impaired, with a mean CGAS score of 15 at index time.

Psychotic symptoms were the most marked symptomatology cluster. Disorganized behavior was present in 82% of patients, and disorganized speech, in 71%. Delusion was manifest in 55%, and hallucination in 37%. The most frequent delusions were of grandiosity (47%),

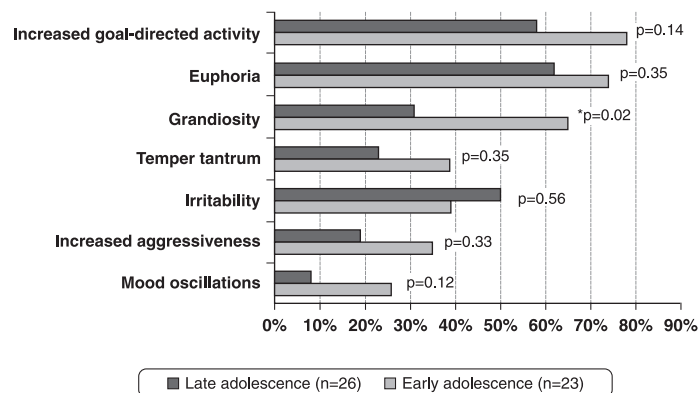


Figure 1 Manic symptoms of patients with bipolar disorder by early (age < 15 years) and late (age ≥ 15 years) adolescence subgroups.

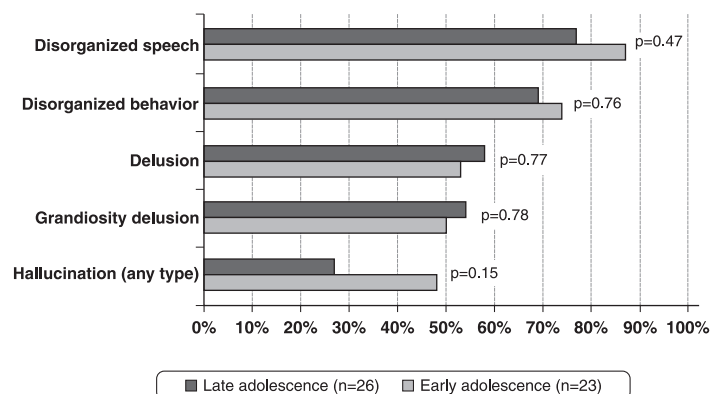


Figure 2 Psychotic symptoms of patients with bipolar disorder by early (age < 15 years) and late (age ≥ 15 years) adolescence subgroups.

and the most common hallucinations were auditory (29%) and visual (16%). The frequency of psychotic symptoms was similar in the early and late adolescent subgroups, and there was no difference between genders (Table 1).

Regarding past psychiatric history, most patients (76%) reported one or more depressive episodes (mean = 2.7; range, one to seven) prior to the first manic episode. Of the 49 subjects, 23 had experienced psychotic symptoms during a previous depressive episode (47%); all of them (n=23; 100%) presented disorganization and 19 (83%) presented symptoms of a psychotic dimension (i.e., hallucinations and/or delusions) during their first manic episode.

Psychomotor alterations during a past depressive episode were also remarkably prevalent; 29% (n=14) had had severe psychomotor retardation during a depressive episode, and 14% (n=7) had been catatonic (Table 2). Of these seven subjects who had exhibited catatonia during a previous depressive episode, all of them (n=7; 100%) presented with disorganization and six (86%) with psychotic symptoms (i.e., hallucinations and/or delusions) during their first manic episode.

Psychomotor retardation during a prior depressive episode was more frequent among the late-adolescent than the early-adolescent group (42 vs. 13%, $p = 0.03$). Even though this difference did not hold up after Bonferroni correction, a trend remained.

Table 1 Frequency of psychotic and manic symptoms among adolescents with bipolar disorder, total sample and comparison between age and gender subgroups

Clinical symptoms	n	Female		Male		Fisher's p
		Early	Late	Early	Late	
n	49	8	16	15	10	
Disorganization						
Disorganized behavior	82	88	75	87	80	0.88
Disorganized speech	71	88	75	67	60	0.62
Psychotic dimension						
Delusion	55	63	44	47	80	0.29
Hallucination, any	37	63	25	40	30	0.32
Hallucination, auditory	29	50	19	33	20	0.40
Hallucination, visual	16	38	13	13	10	0.43
Manic symptoms						
Increased goal-directed activity	67	88	63	73	50	0.37
Euphoria	67	75	69	73	50	0.66
Grandiosity	47	50	31	73	30	0.07
Temper tantrum	31	38	19	40	30	0.60
Irritability	45	38	63	40	30	0.39
Increased aggressiveness	27	38	13	33	30	0.43
Mood oscillations	16	38	6	20	10	0.23

Data presented as %, unless otherwise specified.
Early = age < 15 years; late = age ≥ 15 years.

Table 2 Previous psychiatric history, medication use, and family history of mood disorder in adolescents with bipolar disorder, total sample and stratified by age/gender subgroups

Predictive factors	Total	Female		Fisher's p	Male		Fisher's p		
		Early	Late		Early	Late			
n	49	23	26		8	16	15	10	
Previous major depression	76	74	77	1.00	63	75	80	80	0.80
Psychotic depression	47	39	54	0.39	63	56	27	50	0.28
Depression with catatonia	14	9	19	0.42	13	19	7	20	0.80
Depression with psychomotor retardation	29	13	42	0.03	13	33	13	50	0.15
Depressed with agitation	16	27	8	0.12	25	13	27	0	0.27
SSRI use	18	17	19	1.00	13	25	20	10	0.81
Comorbid ADHD	22	30	15	0.30	13	13	40	20	0.32
Family history									
Major depression	47	52	42	0.57	38	38	60	50	0.60
Bipolar disorder	16	17	15	1.00	13	6	20	30	0.40
Some mood disorder	49	57	42	0.39	50	38%	60%	50%	0.67

Data presented as %, unless otherwise specified.
ADHD = attention-deficit hyperactivity disorder; early = age < 15 years; late = age ≥ 15 years; SSRI = selective serotonin reuptake inhibitor.

The age at onset of first depressive episode was 11.4 years (SD = 5.4; range, 4 to 17 years). The mean time elapsed from the first depressive episode to the first manic episode was 2.5 years (range, 3 months to 7 years). We carried out a survival analysis to estimate the equality of distribution of age at onset of previous depressive episode by age and gender (data not shown), finding that males had a tendency to earlier onset of depressive episode.

Discussion

To the best of our knowledge, this is the first study with a homogeneous clinical sample to investigate the clinical characteristics of a sample of adolescent inpatients with BD in Latin America. The predominance of typical clinical features of BD (e.g., elated mood and grandiosity) presented by our inpatients and their follow-up after hospitalization strengthened the homogeneity and diagnostic reliability of the sample.

Our findings show a high prevalence of disorganization and psychotic symptoms during the first manic episode, as well as frequent occurrence of psychotic depression prior to the first manic episode.

Psychotic symptoms have been reported as a more salient feature in children and adolescents with BD than in adults with the disease since the 1900s.²⁷ In 1984, Joyce²⁸ suggested that there is an inverse relationship between age of onset and presence of psychotic symptoms during first manic episode in patients with BD. McGlashan²⁹ also reported that adolescents with BD displayed significantly more psychotic symptoms (delusions and hallucinations) than adults. However, establishing consistent correlations between the age of onset and occurrence of psychotic symptoms is difficult due to the frequent changes in clinical presentation throughout the different developmental stages.^{6,19,30}

The high frequency of psychotic symptoms manifested by our adolescent inpatients is consistent with similar investigations of early-onset BD.⁷ Some methodological questions may have affected the frequency of reporting of such symptoms in the literature.^{3,19} Consistent with other authors,^{7,8} we understand that the accuracy of psychotic and disorganization symptom recognition is contingent on diagnostic procedures (e.g., patients interviewed directly and face-to-face; clinical experience of the interviewers) and decisions regarding sample selection (e.g., severe inpatients).

Few studies have investigated disorganization symptoms specifically in correlation to both early-onset schizophrenia and BD.^{13,19} Recent studies on dimensional models during the course of the disease have suggested that disorganization may represent an independent dimension (which some authors term the cognitive dimension),¹⁹ which alongside the psychotic dimension (e.g., hallucinations and delusions) and the other two or three dimensions (depressive dimension; negative symptoms dimension; hostility or excitement dimension), make up the symptomatic constellation for the diagnosis of schizophrenia, BD, and other psychotic syndromes.^{18,19,31} The similar occurrence of psychotic symptoms during first manic episode in

both age groups (early and late adolescents) of our sample may suggest that disorganization or psychotic manifestations were not an age-dependent phenomenon, but rather were related to the severity of the disorder, i.e., a BD-specific phenomenon as suggested by Angst.¹¹

Most of our patients presented simultaneous manifestations of manic, psychotic, and disorganized symptoms. This type of BD tends to be confused with schizophrenia or other psychotic disorders, especially in the early stages. During the first psychotic episode, diagnosis can be unstable due to overlap of nonspecific symptoms, such as disorganization and psychotic symptoms.^{14,17,30,32}

Researchers have pointed out that one reason for inefficient differentiation between early-onset BD and early-onset schizophrenia could be the widespread and uncritical diagnosis of schizophrenia whenever psychotic symptoms are present.⁵ Furthermore, Reimherr & McClellan⁶ state that, while disorganization and psychotic symptoms were once considered the hallmark of schizophrenia, negative symptoms seem to be the most specific indicators of early-onset schizophrenia. Fischer & Carpenter Jr.³³ pointed out that psychotic manifestations might be important, but not essential, and recommend the use of secondary criteria related to negative symptoms and mood instability other than disorganization and psychotic symptoms for differential diagnosis between schizophrenia and BD.

Regarding the investigation of psychiatric phenomena as a possible predictive factor of first manic episode, the high rate of occurrence of depressive episodes with psychotic or classic melancholic symptoms reported by our patients is consistent with earlier studies that suggests that a very early-onset depressive episode (before age 13 years) might be a frequent first manifestation of BD. Also, very early-onset psychotic depression may be a predictive factor for subsequent development of BD.^{13,34-36}

The frequent occurrence of psychotic depression in our patients, who subsequently developed first manic episode with disorganization and psychotic features, highlights the possibility that psychosis and disorganization may be more related to specific, BD-related psychopathology and neurobiological dysfunction and less related to the age of onset.^{9,11,13,34,37,38} Further investigations focused on disorganization symptoms during depressive episodes in children and adolescents may help differentiate unipolar depressive episode, BD, and schizophrenia.^{6,20,33}

The predominance of males in the younger developmental subgroup of BD patients in our sample is consistent with similar studies.^{3,5,39} However, the possibility that males in both age groups experienced their first manic episode earlier than females deserves further validation in a larger sample. The scarcity of studies comparing clinical features of BD between children and adolescents of both sexes precludes any conclusion as to whether the predominance of males was due to a true gender difference in age of onset or to a gender difference in symptom expression (e.g., boys with BD may draw more attention to themselves by showing more externalizing behavior than girls and, therefore, are treated earlier because the family environment is more disturbed and academic impairment is more pronounced).

The results of the present study should be viewed in the context of the limitations that follow. As we described patients referred to the child and adolescent psychiatry service of a large university hospital, and all subjects in the present study were inpatients, our findings should not be generalized to other psychiatric sampling frames, nor to community samples.

Because children may not report lifetime psychopathology accurately, all assessments were done in combination with parent or legal-guardian interviews. Thus, data about age of onset and offset of symptoms required retrospective recollection by the child's parent (usually the mother).

Finally, although studies with larger samples are needed to reevaluate the validity of these findings, the small sample size is mainly attributable to the rarity of cases, because of the difficulty in defining diagnosis in this age group, and probably prevented demonstration of major differences in gender and age of onset.

Although the strength of our conclusions is mitigated by the above limitations, our investigation suggests that early-onset BD might be related to a high rate of disorganization and psychotic symptoms.

One of the clinical implications of our study is to cast light on the role of the occurrence of psychotic depression as a predictor of subsequent manic episodes. This warrants further investigation in future studies with larger, more representative samples. A prospective observational cohort of high-risk offspring of BD patients might also be a useful model of investigation.

Another clinical implication of our study is that adolescents with early-onset BD may frequently present with disorganization and psychotic symptoms during manic episodes. We recommend that clinicians consider BD as an alternative diagnosis parallel to schizophrenia when dealing with children and adolescents in first psychotic episode.^{7,14,18} Researchers have called for improved training of practitioners to recognize pathological delusions and hallucinations, as well as different dimensions of a psychotic syndrome in children and adolescents.^{7,13}

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Disclosure

The authors report no conflicts of interest.

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