Developmental Pathways for Different Subtypes of Early-Onset Bipolarity in Youths

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ABSTRACT

Objective: Two main patterns of comorbidity have been described in bipolar disorder in children and adolescents: the first including preexisting attention-deficit/hyperactivity disorder (ADHD) and related disruptive behavior disorders and the second including anxiety disorders, namely, the association of co-occurring multiple anxiety disorders, usually predating the onset of bipolarity. This study was aimed at exploring whether ADHD and multiple anxiety disorders may exhibit different pathways to specific bipolar phenotypes.

Method: We compared 49 youths (7 to 18 years) with bipolar disorder + ADHD without anxiety, 76 youths with bipolar disorder + multiple anxiety disorders without ADHD, and 52 youths with bipolar disorder without ADHD or multiple anxiety disorders who were referred to a third-level hospital and diagnosed according to *DSM-IV-TR* in the period 2005–2011. Subjects were evaluated for current and lifetime Axis I psychiatric disorders by using a structured clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version) and followed up for at least 6 months.

Results: Compared to both patients with bipolar disorder + multiple anxiety disorders and patients with bipolar disorder without ADHD and multiple anxiety disorders, patients with bipolar disorder + ADHD without anxiety were more frequently male, were younger, had an earlier onset of bipolar disorder, had a prevalent chronic course and irritable mood, were more likely to present with a bipolar disorder not otherwise specified diagnosis, had a greater clinical severity and functional impairment, had a manic/mixed index episode, had a higher risk of conduct disorder, and were more resistant to treatments, according to the CGI-Improvement scores ($P < .0001$). Patients with bipolar disorder + multiple anxiety disorders were similar to those with bipolar disorder without ADHD or multiple anxiety disorders, except for a higher rate of diagnosis of bipolar II disorder, more use of antidepressants, and less use of atypical antipsychotics.

Conclusions: The presence of comorbid ADHD versus anxiety disorders is indicative of fundamental differences in the phenomenology of bipolar disorder in youth. While ADHD prior to bipolar disorder is associated with a specific bipolar phenotype, bipolar patients with multiple anxiety disorders are similar to "typical" bipolar patients.

J Clin Psychiatry 2012;73(10):1335–1341

Submitted: *November 1, 2011; accepted March 28, 2012.*
Online ahead of print: *September 4, 2012 (doi:10.4088/JCP.11m07504).*
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Whether juvenile- and adult-onset bipolar disorders are the same or different disorders is still an open question. Clinical phenotypes and boundaries of bipolar disorder in youths are still debated,[1] given the possible developmentally different presentation of the early-onset form compared to adult "standards"[2–8] as well as the high rate of comorbidity.[9–12] The exploration of clinical presentations led to the definition of different phenotypes of bipolarity, not only according to *DSM-IV-TR* categorization (bipolar I and II disorder and bipolar disorder not otherwise specified [NOS]) but also in terms of course (episodic or chronic) and prevalent mood (euphoric or dysphoric-irritable).[7,8] A differentiation between a "narrow" and a "broad" phenotype, according to the full *DSM-IV* criteria has been proposed[13] and recently refined.[1,5,14,15] Within this context, the concepts of severe mood dysregulation and temper dysregulation disorder with dysphoria have been temporarily conceptualized in order to define these "nosological orphans."[1,15]

Regarding comorbidity, 2 broad patterns have been described. The first pattern includes preexisting attention-deficit/hyperactivity disorder (ADHD),[11,16–18] with rates ranging from 30% to 90%. The second pattern of comorbidity includes anxiety disorders.[9,12,19,20] According to Sala et al,[12] 44% of a series of 446 bipolar youths met criteria for at least an anxiety disorder. Multiple anxiety disorders have been more closely related to bipolarity.[19,21–23] This relationship may also explain the early finding that the offspring of adult bipolar probands often initially receive anxiety disorder diagnoses.[24,25] These findings are consistent with more recent studies addressing psychopathology in offspring of bipolar parents, who present high rates of ADHD, separation anxiety disorder, generalized anxiety disorder, and social phobia in early or middle childhood and obsessive-compulsive disorder, panic disorder, and bipolar disorder in adolescence.[25]

The aim of the present study was to explore whether early-onset comorbidity is related to specific clinical bipolar phenotypes in terms of age at onset, *DSM-IV* categorization, course, prevalent mood, pattern of comorbidity, and response to treatments. From a large sample of children and adolescents with a diagnosis of bipolar disorder, consecutively referred in the last 7 years, we selected 2 groups of patients according to the presence of ADHD or multiple anxiety disorders prior to bipolar disorder, defined as the current comorbidity with at least 2 anxiety disorders among the following: separation anxiety disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and specific phobias. We hypothesized that these 2 comorbidities may represent different pathways to bipolarity, leading to different clinical bipolar phenotypes. In order to explore this hypothesis,

Clinical Points

- The presence of comorbid attention-deficit/hyperactivity disorder (ADHD) versus anxiety disorders should be actively explored, as it is indicative of fundamental differences in the phenomenology of bipolar disorder in youths.
- ADHD plus bipolar disorder might represent a distinct early-onset phenotype within the bipolar spectrum.

we compared youths with bipolar disorder + ADHD, bipolar disorder + multiple anxiety disorders, and bipolar disorder without ADHD or multiple anxiety disorders.

METHOD

Patients

Our naturalistic study is based on a clinical database of 282 youths, aged 7 to 18 years (mean ± SD age = 13.3 ± 2.7 years), who were referred to our third-level hospital with a nationwide catchment area in the period 2005–2011 and who met *DSM-IV-TR* criteria for bipolar I or II disorder or bipolar disorder NOS. Part of this sample (54 patients) was included in previous studies. Subjects were evaluated for current and lifetime Axis I psychiatric disorders at intake by using historical information, a diagnostic interview, the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version (K-SADS-PL),[26] and prolonged observations of interactions with peers, parents, and/or examiners. Behavioral and social-emotional skills were observed directly by trained psychiatrists during interactive activities throughout the diagnostic phase. Inclusion criteria included number of symptoms, duration, and degree of impairment, according to Clinical Global Impressions-Severity of illness scale (CGI-S)[27] score ≥ 4 and Children's Global Assessment Scale (C-GAS)[28] score ≤ 60. All patients with mental retardation, pervasive developmental disorders, and schizophrenia were excluded. Details on the diagnostic procedure can be found elsewhere.[8] Thirty-five patients were randomly selected to establish the interrater reliability. A good interrater reliability for diagnosis of bipolar disorder (including the categorization in bipolar I disorder, bipolar II disorder, and bipolar disorder NOS) and other comorbid disorders with K-SADS-PL was found in this study: ie, κ coefficients of agreement higher than 0.75 (mean κ = 0.85, κ value for bipolar disorder = 0.82).[7]

On the basis of this diagnostic procedure, 49 bipolar patients presented a bipolar disorder + ADHD without current or lifetime comorbidity with anxiety disorders (bipolar disorder + ADHD group), 76 bipolar patients presented a comorbidity with at least 2 anxiety disorders (multiple anxiety disorder) without current or lifetime ADHD (bipolar disorder + multiple anxiety disorders group), and 52 bipolar patients did not present current or lifetime ADHD and anxiety disorders (bipolar disorder group).

Among the total sample of 282 bipolar patients, 96 (34.0%) presented a current comorbidity with ADHD, 181 (64.2%) presented a current comorbidity with at least 1 anxiety disorder, and 52 (18.4%) did not present current or lifetime ADHD and anxiety disorders. In order to remove the overlap between the first 2 groups, the 47 patients (16.7%) with co-occurring current or lifetime ADHD and anxiety disorder were excluded. On the basis of this procedure, 134 patients presented a comorbidity with at least 1 anxiety disorder without current or lifetime ADHD, 76 patients presented a current comorbidity with at least 2 anxiety disorders without current or lifetime ADHD, and 49 patients presented a bipolar disorder + ADHD without current or lifetime comorbidity with anxiety disorders. Thus, 76 patients were included in the group bipolar disorder + multiple anxiety (without ADHD), 49 in the group bipolar disorder + ADHD (without anxiety), and 52 in the group bipolar disorder (without ADHD or anxiety disorders).

All patients were categorized into groups according to course (episodic or chronic) and the prevalent mood. According to the prevalent mood, 2 groups have been described. The first includes patients with elated mood and/or euphoria and/or inflated self-esteem/grandiosity irrespective of the presence or absence of irritable mood (euphoric group); the second includes patients with irritable mood but not elated mood and/or euphoria and/or inflated self-esteem/grandiosity (irritable mood). The episodic/chronic and euphoric/irritable distinctions were made by the first author (G.M.) and each of the psychiatrists who administered the clinical interview and directly participated in the diagnostic process. A good interrater reliability was found, with κ coefficients of agreement higher than 0.80.[7]

Because the symptom criteria for ADHD and mania/hypomania overlap, in order to disentangle the 2 disorders, we considered an indicator of mood disorder to be the presence of clear euphoria/grandiosity/elated mood; very rapid alternations between manic and depressive symptoms, even when they did not meet duration criteria for manic or depressive symptoms; or an abnormal mood (sadness, anger, episodic irritability) and hyperarousal associated with a minimum of 3 manic symptoms (1 less symptom than required by the *DSM-IV* B criterion).[8]

The severity of the illness was recorded at baseline by CGI-S score. Functional impairment was assessed during the same visits by using the C-GAS on a scale from 0 (severe impairment) to 100 (superior functioning). Patients were followed up for at least 6 months with monthly visits. During the period of observation, all patients were naturalistically treated with valproic acid and/or lithium and/or atypical antipsychotics. Antidepressants were used only in association with mood stabilizers when depressive symptoms did not improve after mood stabilization (at least 8 weeks) or when anxiety disorders were particularly impairing. Patients were considered responders when they presented, after a

Table 1. Demographic and Clinical Features of Children and Adolescents With Bipolar Disorder With ADHD, With Bipolar Disorder With Multiple Anxiety Disorders, and With Bipolar Disorder Without ADHD or Multiple Anxiety Disorders

	Bipolar Disorder					
Feature	With ADHD (n = 49)	With Multiple Anxiety Disorders (n = 76)	Without ADHD or Multiple Anxiety Disorders (n = 52)	F/χ^2	*df*	*P*
Male sex, n (%)	40 (81.6)	34 (44.7)	33 (63.5)	17.2	2	.0001***
Age, mean (SD), y	12.5 (2.9)	14.5 (2.6)	14.6 (2.6)	10.2	176	<.0001***[a]
Age at onset, mean (SD), y	8.4 (2.4)	11.1 (3.0)	11.3 (3.0)	17.0	176	<.0001***[a]
Prebubertal onset (< 12 ys), n (%)	45 (91.8)	43 (56.6)	32 (61.5)	18.3	2	<.0001***
Follow-up, mean (SD), mo	11.3 (1.8)	11.0 (2.0)	11.7 (1.6)	2.2	176	.109
CGI-S baseline score, mean (SD)	5.7 (0.7)	5.1 (1.0)	5.3 (0.7)	7.6	176	<.0001***[a]
CGI-I score, mean (SD)	2.8 (0.8)	2.1 (0.8)	2.4 (0.8)	11.4	176	.001***[a]
C-GAS baseline score, mean (SD)	38.2 (4.7)	41.8 (6.3)	41.5 (5.1)	10.6	173	<.0001***[a]
Responders, n (%)	18 (36.7)	57 (75.0)	29 (55.8)	18.3	2	<.0001***
Bipolar I disorder, n (%)	16 (32.7)	23 (30.3)	26 (50.0)	5.7	2	.059
Bipolar II disorder, n (%)	10 (20.4)	47 (61.8)	19 (36.5)	22.1	2	<.0001***
Bipolar disorder NOS, n (%)	23 (46.9)	6 (7.9)	7 (13.5)	30.2	2	<.0001***
Chronic course, n (%)	33 (67.3)	19 (25.0)	17 (32.7)	23.7	2	<.0001***
Irritable mood, n (%)	32 (65.3)	22 (28.9)	22 (42.3)	16.1	2	<.0001***
Psychotic symptoms, n (%)	10 (20.4)	14 (18.4)	20 (38.5)	7.4	2	.025*
Index episode manic/mixed, n (%)	39 (79.6)	35 (46.1)	29 (55.8)	14.0	2	<.0001***

[a]Bipolar disorder + ADHD versus bipolar disorder + anxiety and bipolar disorder + ADHD versus bipolar disorder (Tukey test).
*P < .05, ***P < .002 (Bonferroni correction).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, C-GAS = Children's Global Assessment Scale, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of illness scale, NOS = not otherwise specified.

6-month follow-up, a CGI-Improvement score of 1 or 2 (very much improved or much improved), a CGI-S score ≤ 3, and a C-GAS score > 60 for at least 3 further consecutive monthly visits.

All the patients and their families participated voluntarily in the study after written informed consent was obtained for assessment and treatment procedures. The study was approved by the ethical committee of our hospital.

Statistical Analyses

Subjects were compared by using χ^2 analysis on categorical variables, analysis of variance on continuous variables, and Tukey post hoc comparisons on continuous variables. However, owing to the multiple comparisons and the number of patients, our results are prone to both type I and type II errors. Therefore, we used Bonferroni correction for multiple comparisons, setting significance at .002 level, 2-tailed.

RESULTS

As reported in Table 1, patients with bipolar disorder + ADHD were more frequently male (81.6% vs 44.7% in bipolar disorder + multiple anxiety disorders and 63.5% in bipolar disorder patients without ADHD or multiple anxiety disorders, P < .0001), were significantly younger (12.5 ± 2.9 years vs 14.5 ± 2.6 and 14.6 ± 2.6 in the other 2 groups, P < .0001), and presented an earlier onset of the disorder (8.4 ± 2.4 years vs 11.1 ± 3.0 and 11.3 ± 3.0 in the other groups, P < .0001), with a prepubertal onset in 91.8% of patients compared to the 56.6% in the group with bipolar disorder + multiple anxiety disorders and 61.5% in the bipolar disorder patients without ADHD or multiple anxiety disorders (P < .0001). Patients with bipolar disorder + ADHD had higher levels of clinical severity (CGI-S scores) (5.7 ± 0.7 vs 5.1 ± 1.0 in bipolar disorder + multiple anxiety disorders and 5.3 ± 0.7 in bipolar disorder patients without ADHD or multiple anxiety disorders, P < .0001) and functional impairment (C-GAS) (38.2 ± 4.7 vs 41.8 ± 6.3 and 41.5 ± 5.1 in the other groups, P < .0001). Response to treatment was poorer in the bipolar disorder + ADHD group, in terms of both CGI-I score (2.8 ± 0.8 vs 2.1 ± 0.8 and 2.4 ± 0.8 in the other 2 groups, P = .001) and rate of responders (36.7% vs 75.0% and 55.8% in the other 2 groups, P < .0001). Of note, Tukey post hoc comparisons on continuous variables showed that patients with bipolar disorder + ADHD significantly differed from those with bipolar disorder + multiple anxiety disorders and those with bipolar disorder without ADHD or multiple anxiety disorders, while the last 2 groups did not differ according to the selected parameters.

While rate of bipolar I disorder was similar in the 3 groups, patients with bipolar disorder + ADHD more frequently had a bipolar disorder NOS diagnosis (46.9% vs 7.9% and 13.5% in the other groups, P < .0001), while bipolar II disorder was less frequent in bipolar disorder + ADHD and more frequent in bipolar disorder + multiple anxiety disorders (20.4% in bipolar disorder + ADHD, 61.8% in bipolar disorder + multiple anxiety disorders, 36.5% in bipolar disorder without ADHD or multiple anxiety disorders, P < .0001).

Patients with bipolar disorder + ADHD presented the highest frequency of chronic course (67.3% vs 32.7% episodic) (P < .0001) and irritable mood (65.3% vs 34.7%

Table 2. Current and Lifetime Comorbidities in Children and Adolescents With Bipolar Disorder With ADHD, With Bipolar Disorder With Multiple Anxiety Disorders, and With Bipolar Disorder Without ADHD or Multiple Anxiety Disorders

	Bipolar Disorder				
Comorbidity, n (%)	With ADHD (n = 49)	With Multiple Anxiety Disorders (n = 76)	Without ADHD or Multiple Anxiety Disorders (n = 52)	χ^2_2	*P*
Generalized anxiety disorder	0 (0.0)	55 (72.4)	0 (0.0)		
Separation anxiety disorder	0 (0.0)	39 (51.3)	0 (0.0)		
Panic disorder	0 (0.0)	43 (56.6)	0 (0.0)		
Social phobia	0 (0.0)	43 (56.6)	0 (0.0)		
Simple phobia	0 (0.0)	22 (28.9)	0 (0.0)		
Obsessive-compulsive disorder	12 (24.5)	37 (48.7)	18 (34.6)	7.7	.021*
ADHD	49 (100)	0 (0.0)	0 (0.0)		
Oppositional defiant disorder	18 (36.7)	10 (13.2)	10 (19.2)	10.0	.007*
Conduct disorder	23 (46.9)	2 (2.6)	11 (21.2)	36.1	<.0001***

*$P < .05$, ***$P < .002$ (Bonferroni correction).
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Table 3. Treatment Comparisons in Children and Adolescents With Bipolar Disorder With ADHD, With Bipolar Disorder With Multiple Anxiety Disorders, and With Bipolar Disorder Without ADHD or Multiple Anxiety Disorders

	Bipolar Disorder				
Treatment, n (%)	With ADHD (n = 49)	With Multiple Anxiety Disorders (n = 76)	Without ADHD or Multiple Anxiety Disorders (n = 52)	χ^2_2	*P*
Antidepressants	11 (22.4)	40 (52.6)	16 (30.8)	13.1	.001***
Valproic acid	38 (77.6)	54 (71.1)	25 (48.1)	11.2	.004*
Lithium	24 (49.0)	22 (28.9)	27 (51.9)	8.4	.015*
Valproic acid + lithium	11 (22.4)	5 (6.6)	7 (13.5)	6.7	.036*
Atypical antipsychotics	25 (51.0)	16 (21.1)	23 (44.2)	13.7	.001***
Methylphenidate	16 (32.7)	0 (0.0)	0 (0.0)		
Psychotherapy	23 (46.9)	36 (47.4)	20 (38.5)	1.1	.566

*$P < .05$, ***$P < .002$ (Bonferroni correction).

elated) ($P < .0001$). Interestingly, in 79.6% of patients with bipolar disorder + ADHD compared to 46.1% and 55.8% in the other groups, the index episode was manic/mixed ($P < .0001$). The rate of psychotic symptoms did not differ significantly among the 3 groups.

Pattern of comorbidity significantly differentiated the 3 groups (Table 2). Subjects with bipolar disorder + ADHD presented the highest rate of disruptive behavior disorder comorbidity, namely, conduct disorder (46.9% vs 2.6% and 21.2% in the other groups, $P < .0001$).

Regarding treatments (Table 3), patients with bipolar disorder + multiple anxiety disorders more frequently used antidepressants (52.6% vs 22.4% in bipolar disorder + ADHD and 30.8% in bipolar disorder without ADHD or multiple anxiety disorders, $P = .001$) and less frequently used atypical antipsychotics (21.1% vs 51.0% in bipolar disorder + ADHD and 44.2% in bipolar disorder without ADHD and multiple anxiety disorders). Of course, stimulants were used only in the patients with bipolar disorder + ADHD. The rate of psychotherapy was similar among groups.

DISCUSSION

Comorbid conditions prior to bipolar disorder may be an additional important differential feature of bipolar disorder.[29–31] Pattern of comorbidity in early-onset bipolar disorders are related to 2 broad categories: ADHD and other disruptive behavior disorders on the 1 side and multiple anxiety disorders on the other. And both of these comorbidities usually predate the onset of bipolarity.[16,17,23]

Our results indicate that these different precursors to bipolarity are associated with well-distinct phenotypes. Patients with ADHD prior to bipolar disorder are more frequently male (probably as a consequence of the uneven gender distribution in ADHD patients), have an earlier onset of bipolar symptoms, have a prevalent chronic course and an irritable/dysphoric mood, are more likely to have bipolar disorder NOS, and usually have an index episode that is manic/mixed. A frequent complication is with other disruptive behavior disorders, namely, the most troublesome conduct disorder. Patients with these disorders present a poorer response to treatments, consistent with previous meta-analyses.[32] They fit diagnostic criteria for bipolar disorder, although with some atypical features (ie, very rapid alternations between manic and depressive symptoms, or sadness and anger associated to hyperarousal and manic symptoms). Their symptomatology may be hardly attributed to the ADHD or oppositional defiant disorder domains, even at the highest degree of severity.

On the opposite side, patients with an internalizing phase centered on multiple anxiety disorders prior to bipolar disorder have a later onset of the disorder, with prevalent

episodic course and elated mood, and their index episode can be either manic/mixed or depressive. Consistent with other findings,[12] they more frequently have bipolar II disorder. Data indicate also that they may be more responsive to pharmacologic treatments, according to the lower CGI-I score. These patients are more typical in terms of (episodic) course and (elated) mood compared to the bipolar disorder + ADHD group and similar to bipolar youths without ADHD or multiple anxiety disorders. Furthermore, they present a more frequent use of antidepressants and a less frequent use of atypical antipsychotics (probably due to a lesser severity). The frequent use of antidepressants is not surprising, given that patients with bipolar II disorder spent significantly more time with syndromal or subsyndromal depressive symptoms[10] and have frequent anxiety comorbidities. The risk of mood destabilization or (hypo)manic switches under antidepressant treatment in bipolar II disorder is still debated in adult patients,[33,34] while data in children and adolescents are still scarce.[35] A close monitoring of possible worsening after antidepressant monotherapy, such as irritability, behavioral dyscontrol, substance abuse, erratic life, and suicide risk, is warranted.

It may be debated whether these 2 comorbidities really represent "different pathways" to early-onset bipolarity. In our patients, as well as in other reports, both ADHD and multiple anxiety disorders preceded the onset of the bipolar symptoms, and they may be considered at least precursors or risk factors for subsequent bipolarity or, not alternatively, markers for different mood disorders within the bipolar spectrum. However, other early comorbidities may be relevant in affecting occurrence and features of bipolar disorder, such as the autism spectrum disorders, associated with a higher risk of bipolar disorder with psychotic symptoms.[36]

The underlying issue is whether these subtypes represent different disorders. Our data suggest that, while the bipolar disorder + multiple anxiety disorders group is similar to all the other bipolar patients without anxiety or ADHD comorbidity, bipolar disorder + ADHD is associated with a specific phenotype in terms of course and clinical presentation. This specificity has been recently supported by a magnetic resonance imaging study comparing striatal volumes (caudate, putamen, and globus pallidus) of youths from 4 groups: bipolar disorder with comorbid ADHD, bipolar disorder without comorbid ADHD, ADHD alone, and healthy control subjects.[37] The presence or absence of comorbid ADHD in patients with bipolar disorder was associated with distinct alterations in caudate volumes, suggesting that these groups have different, but related, mechanisms of neuropathology.

Further support for the specificity of ADHD + bipolar disorder comes from longitudinal studies. Adult bipolar patients with a history of childhood ADHD compared with bipolar patients without a history of ADHD have an earlier onset of their first affective episode, more frequent affective episodes, and more interpersonal violence, regardless of whether the ADHD symptoms remained in adulthood or not.[38] Consistently, Bernardi and coworkers[11] showed that adult patients with bipolar disorder plus ADHD, both persistent in adulthood or remitted, reported a significantly earlier onset of mood disorder, higher number of previous mood episodes, and significantly higher impulsivity than bipolar disorder patients without ADHD. Both these studies suggest that ADHD + bipolar disorder might represent a distinct early-onset phenotype of bipolar disorder.

Long-term naturalistic prospective studies might represent an important source of information, and the present findings are therefore of particular relevance to clinical practice in child and adolescent bipolar disorder. Prospective follow-up studies may clarify whether these children with different phenotypes may crystallize their symptomatology into a more classic (affective and episodic) presentation as they grow up or if they retain their "atypical" presentation or follow different pathways, mainly toward disruptive behavior disorders or depressive disorders.[14] The recent debate regarding the nosologic status of bipolar disorder NOS and the differentiation of putative clinical conditions, such as severe mood dysregulation and temper dysregulation disorder with dysphoria, may help to study more homogeneous populations and to explore possible biological, neuropsychological, and environmental features underlying these clinical pictures.[15]

Our naturalistic study presents several methodological limitations. First, only subjects referred to our third-level hospital who usually needed pharmacologic treatment were included, and this selection bias may limit the generalization of the conclusions, because our sample may represent a subgroup of more severely impaired subjects in terms of clinical presentation, pattern of comorbidity, and response to treatments. The subgrouping was based on clinical grounds. Only a selected number of features were considered as relevant, and the diagnostic exploration did not include other potentially important elements. Age at onset of bipolar disorder was assessed retrospectively and was based on historical information and previous clinical reports. In patients with ADHD prior to bipolar disorder and frequent comorbid oppositional defiant disorder or conduct disorder, it may be particularly difficult to define the precise onset of the mood disorder. Furthermore, the severity of the behavioral symptoms may have anticipated the referral, and this factor may have further affected the reconstruction of the exact onset of bipolar disorder. Keeping these issues in mind, we were particularly careful in defining the onset of bipolar disorder and comorbid disorders.

Another limitation is that we have used the outcome measure CGI, which is not a specific measure of bipolar disorder severity and improvement. Considering the high level of comorbidity in bipolar disorder, it may be difficult to disentangle the specific contribution of the co-occurring disorders (particularly ADHD and oppositional defiant disorder or conduct disorder) to the severity of symptomatology, as well as the specific effect of pharmacotherapy on manic/mixed symptoms. However, there is evidence that global ratings can be more sensitive to change during acute treatment

than scores on itemized symptom rating scales.[39,40] Furthermore, the CGI-I criterion corresponds to what clinicians use to determine whether to continue or interrupt a medication trial. In a naturalistic setting with unselected patients, characterized by high co-occurrence and changeability, an apparent improvement of 1 symptom, considered alone, may be consequent to a worsening of another symptom. For this reason, the course of the clinical picture as a whole is more reliably captured by a more global measure.

A better knowledge of the pathways leading to early mood disorders may increase our capacities for a possible prevention or at least a timely recognition in youths with internalizing or externalizing symptoms, with positive implications on both prognosis and treatment.[3] Given that the occurrence of comorbid ADHD has an impact on the long-term course of bipolar disorder,[11,37] further longitudinal studies may explore whether a timely treatment of ADHD may affect the outcome of some key features of bipolar disorder, such as frequency of episodes, and occurrence of impulsivity, violence, and hostility.

Drug names: lithium (Lithobid and others), methylphenidate (Daytrana, Ritalin, and others), valproic acid (Stavzor, Depakene, and others).

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Potential conflicts of interest: **Dr Masi** has served on advisory boards for Eli Lilly, Shire and Novartis; has received research grants from Eli Lilly and Shire; and has been speaker for Eli Lilly, Shire, Sanofi-Aventis, and Novartis. **Dr Pfanner** has received research grants from and has been speaker for Eli Lilly. **Dr Perugi** has served on advisory boards for Sanofi-Aventis, AstraZeneca, Janssen-Cilag, Lundbeck, BMS Otsuka and Eli Lilly; and has received grants from AstraZeneca, Eli Lilly, and Lundbeck. **Drs Mucci**, **Berloffa**, and **Magazù** do not have conflicts of interest to declare.

Funding/support: None reported.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.