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Irritability Without Elation in a Large Bipolar Youth Sample: Frequency and Clinical Description

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Abstract

Objective—To determine whether some children with bipolar disorder (BP) manifest irritability without elation and whether these children differ on socio-demographic, phenotypic, and familial features from those who have elation and no irritability and from those who have both.

Method—361 BP youth recruited from three sites, University of Pittsburgh, Brown, and UCLA were assessed at baseline and for most severe past symptomatology using standardized semi-structured interviews. BP subtype was identified and frequency and severity of manic symptoms quantified. Subjects were required to have episodic mood disturbance to be diagnosed with BP. The sample was then re-classified, and compared, based upon the most severe lifetime manic episode into three subgroups: elated only, irritable only, and both elated and irritable.

Results—Irritable only and elated only subgroups constituted 10% and 15% of the sample, respectively. Except for the irritable only subjects being significantly younger than the other two subgroups, there were no other between groups socio-demographic differences. There were no significant between-group differences in the BP subtype, rate of psychiatric comorbidities, severity of illness, duration of illness, and family history of mania in first/second-degree relatives and other psychiatric disorders in first degree relatives with the exception of depression and alcohol abuse occurring more frequently in the irritability only subgroup. The elated only group had higher scores on most DSM-IV mania criterion B items.

Conclusions—The results of this study support the DSM-IV A criteria for mania in youth. Irritable-only mania exists, particularly in younger children, but similar to elated-only mania it occurs infrequently. The fact that the irritable only subgroup has similar clinical characteristics and family histories of BP, as compared to subgroups with predominant elation, provides support for continuing to consider episodic irritability in the diagnosis of pediatric BP.

Introduction

Unique, age specific aspects of the pediatric bipolar disorder (BP) phenotype continue to be debated. According to the DSM-IV¹ criteria, irritability and elation are core features of the pathological alteration in affect and mood in the manic phase of bipolar disorder, but there is no consensus on the differential significance of these symptoms in children and adolescents.²⁻¹² In this regard, a recent series of reports^{13,14}, documenting a dramatic rise in the reported cases of bipolar illness among children and teens, underscores growing concern with diagnostic error in this age group and, accordingly, the need for rigorous, empirical research to illuminate unique psychopathological features of these core elements. While some assert that severe, explosive irritability is more common in bipolar children than euphoria or elation^{2-5,12} Geller and colleagues,^{9,15} taking note of potential overlap in diagnostic symptoms between early childhood bipolar illness and multiple other forms of severe childhood psychopathology, have argued for the diagnostic centrality of elation and/or grandiosity in research of pediatric bipolar disorder in order to minimize risk of diagnostic imprecision. Notably, in a review and meta-analysis of seven studies, with differing methodologies, of juvenile bipolar subjects completed between 1982 and 2004, Kowatch and colleagues¹⁶ report that rates of irritability and elation vary widely across study samples.

In an attempt to define diagnostic boundaries more sharply, Leibenluft and colleagues¹⁷ have operationalized three clinical phenotypes of bipolar disorder: narrow, intermediate, and broad. Narrow phenotype bipolar disorder is defined as a child having at least one episode in which full DSM-IV criteria are met, including duration criteria and the presence of elation and/or grandiosity. The intermediate phenotype has two subtypes: 1) mania or hypomania NOS (episodes too short to meet DSM-IV duration criteria) and 2) irritable mania or hypomania. Broad phenotype children are characterized by chronic irritability and hyperarousal but specifically exclude patients with elation, grandiosity, and decreased need for sleep. Importantly, this same research group has also subtyped irritability according to course

(chronic vs. episodic) and found that episodic irritability was associated with bipolar disorder and anxiety while chronic irritability, or broad phenotype, was more closely associated with ODD, CD, and ADHD and possible increased risk to develop MDD.¹⁸

Other recent reports further underscore the potential importance of distinguishing irritability and elation within the pediatric bipolar spectrum. Rich and colleagues compared subjects with disruptive behavior disorders (DBDs) and severe mood dysregulation to narrow phenotype bipolar subjects and found differences in psychophysiological measures, thus indicating that the biological substrate of irritability may vary between diagnostic groups.¹⁹ Brotman and colleagues have compared parents of youth with DBDs and severe mood dysregulation to parents of youth with narrow phenotype bipolar disorder, finding that bipolar disorder was significantly more likely in parents of narrow phenotype bipolar disorder.²⁰ Masi and colleagues reported on 136 BP-I patients (40% female) with mean age of 13.5 who were clinically sub-typed into chronic vs. episodic course and “prevalent elated” vs “prevalent irritable” and found that elated mood was more frequent in patients with an episodic course while irritable mood was more frequent in patients with a chronic course.²¹

Reflecting these disparate observations and commentary, the National Institute of Mental Health Research Roundtable on Pre-pubertal Bipolar Disorder²² has advocated further clinical observational research to extend our knowledge of the correlates and predictive value of these symptoms. Thus, at this time the differential significance of irritability versus elated mood with regard to factors such as disease course, psychosocial adjustment, non-affective diagnostic comorbidity, and treatment response remains conjecture.

The main goals of this study were to determine whether mania/hypomania in youth may be manifested with only irritability without elation and whether children with bipolar disorder who have irritability and no elation differ on socio-demographic, phenomenological, and familial features from those who have elation and no irritability and from those who have both. The most severe lifetime symptoms (at intake or in the past) were chosen because of the increased likelihood that these symptoms would be better remembered by parents and youth. The main hypotheses tested in this study are that, as indicated in the DSM-IV, BP may be manifested with irritability without elation and that groups formed based upon the presence or absence of irritability or elation will not differ when compared socio-demographically, phenomenologically, and with regard to family history during the most severe lifetime manic episode. An absence of a difference between the groups would add support for the equal importance of these symptoms in the diagnosis of BP and support the inclusion of subjects with irritable mania in future research studies of pediatric BP.

The participants were subjects enrolled in the Pittsburgh, Brown, UCLA multisite study, “Course and Outcome of Bipolar Illness in Youth” (COBY), which is investigating the long-term psychopathological course, outcome, and effectiveness of naturalistic treatment exposure in pediatric BP. The sample is ideally suited for this investigation because of the large sample, the rigorous application of diagnostic criteria, the availability of family history data, and the enrollment of all subjects in long term prospective follow-up assessments. Additionally, the large size of the COBY sample allows for the formation of mood consistent subgroups categorized by the most severe lifetime manic episode which allows for the investigation of the above hypotheses. Since COBY is following all subjects, future studies will be able to evaluate the above-noted hypotheses prospectively and the stability the manic symptoms overtime.

Methods

Subjects

This report is limited to a sub-sample of the study (N=361), all of whom were administered the K-SADS MRS about the most serious past episode. The study sample of 446 subjects were enrolled at three academic medical centers: Brown University (n= 144), University of California Los Angeles (UCLA; n=90), and University of Pittsburgh Medical Center (UPMC; n=212). Detailed descriptions of the baseline phenomenology can be found in previously published reports.^{23,24} Briefly, most subjects were referred from outpatient programs (66%); 15% of the subjects were recruited from inpatient units, 14% from advertisements and 5% from other sources. Study inclusion criteria included: (1) current age of 7 years 0 months to 17 years 11 months and (2) meets DSM-IV criteria for bipolar I or bipolar II disorder, or the COBY established criteria for bipolar disorder NOS. Two hundred twenty-six subjects met criteria for BP-I, while 20 subjects met criteria for BP-II and 115 for BP-NOS. Since the DSM definition of BP-NOS is not operationalized, to avoid entering into the study youth with “soft” BP symptoms, only children with certain minimum duration plus a minimum number of symptoms with and without prior episodes of depression were considered for the diagnosis of BP-NOS. BP-NOS was defined as the presence of elated mood, plus two associated manic symptoms, or irritable mood plus three DSM-IV associated manic symptoms, along with a change in the level of functioning, duration of a minimum of 4 hours within a 24-hour period, and at least 4 cumulative lifetime days meeting the criteria. Children and adolescents meeting this more strictly defined BP-NOS have similar, but less severe, clinical picture, comorbid disorders, family history, and longitudinal outcome than the BP-I subjects.^{23,24} Moreover, about 25% of these youth diagnosed with BP-NOS converted into BP-I or BP-II over an average period of two years.²³

Study exclusion criteria were: current or lifetime DSM-IV diagnosis of Schizophrenia, Mental Retardation, Autism or severe autistic spectrum disorders, or Mood Disorders due to substance abuse, a medical condition, or secondary to use of medications (e.g., corticosteroids). Subjects determined to have a chronologically primary bipolar disorder with secondary substance abuse disorder were included into the study.

Informed consent was obtained prior to initiation of the assessment from the subject's parent/guardian and from subjects aged 14 years or older. The study procedures were explained in age-appropriate language to younger subjects and verbal assent was obtained prior to the assessment. The institutional review boards at the three centers reviewed and approved the study protocol prior to enrollment of any subject.

Subject Assessment

Socio-demographics—Socioeconomic status was measured using the Hollingshead four-factor scale.²⁵ Pubertal status was reported by subjects of age 10 years and older using the Pubertal Developmental Scale (PDS).²⁶ Subjects aged 7 to 9 completed the PDS with their parent's assistance. The PDS ratings were converted into associated Tanner Stages of sexual development.²⁷ Subjects whose ratings were equivalent to Tanner Stage I or who were younger than age 8 were considered pre-pubertal.

Psychiatric Diagnosis—Subjects were assessed by semi-structured interviews of the child/adolescent and a parent/primary caregiver (about the subject) by bachelor's, master's, and doctoral-degree level clinicians. Non-mood psychiatric disorders were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (KSADS-P/L).²⁸ As the KSADS-PL only ascertains the presence or absence of symptoms, mood symptom criteria were assessed using the depression section of the

KSADS-P (Present Episode, 4th revision) and the KSADS-Mania Rating Scale (KSADS-MRS) to more accurately ascertain the severity of mood symptomatology.²⁹ Manic symptomatology and severity thresholds were updated to reflect the current thinking regarding evaluation of mania/hypomania in youth.³⁰ The KSADS –MRS is a 15 item inventory with excellent inter-rater reliability (intraclass correlation coefficient =.97), convergent validity with Clinical Global Impressions Severity Scale ($r_s=.91$), and differentiates bipolar patients with from those without significant manic symptoms.³¹ Items on the KSADS-MRS are derived from the KSADS-Present Episode 1986 version and includes a mood lability item. Symptoms are rated from 1 (normal or not present) to 6 (extreme symptoms). Mild elation (rated as 3 on this scale) reflects the presence of a “definitely elevated mood and optimistic outlook that is somewhat out of proportion to his/her circumstances”. Mild irritability (rated as 3 on this scale) reflects the presence of “Often (at least 3X/3 hrs. ea. week) feels definitely more angry, irritable than called for by the situation, relatively frequent but never very intense. Or often argumentative, quick to express annoyance. No homicidal thoughts;” (For further information regarding the items included in the K-MRS see www.wpic.pitt.edu/research, under ‘Assessment Instruments’).

Depressive and manic symptom severity ratings were recorded for the most severe week in the month prior to the intake assessment. Subjects were not required to be in an episode of mania or depression at the time of intake. The most severe week of depressive and manic symptomatology in the subject's lifetime was assessed using the KSADS-P/L with the first 84 subjects enrolled in the study, and the KSADS-MRS and KSADS-P/L mood disorder sections for the remaining subjects. Subjects were asked about all lifetime mania or hypomanic episodes but only the most severe and the current (within the last month) were rated. Mood symptoms that overlap with other psychiatric disorders (i.e. motor hyperactivity, distractibility) were not rated as present in the mood sections unless they intensified with the onset of abnormal mood. Comorbid diagnoses were not assigned in COBY if they occurred exclusively during a mood episode. The onset of the first and the most recent episode of each type of DSM-IV major mood episode (manic, mixed, hypomanic, or major depressive episodes) were recorded, as well as the first time subjects met criteria for BP-NOS. The age of onset for a subject's BP-spectrum illness was defined as the age of onset of clinically significant manic, hypomanic, and/or depressive symptoms that affected the child's functioning. Illness duration was defined as the subject's current age minus the age of BP onset. However, given the controversies diagnosing BP in very young children, the minimum age of onset for BP-spectrum illness was arbitrarily set at age 4.

All interviewers and doctoral-level clinicians underwent training and certification in the Schedule for Affective Disorders and Schizophrenia for School –Age Children (K-SADS) at each site. All cases were discussed during weekly clinical consensus team meetings at each site to confirm the diagnoses. This clinical consensus team consisted of doctoral-degree-level child psychiatrists and/or psychologists and the interviewers. During this meeting the K-SADS symptoms and the subject's medical records were reviewed. A best estimate clinical consensus procedure was used to confirm the child psychiatric diagnosis.^{23,24} Additionally, diagnostic issues that could not easily come to consensus were conferenced across the 3 sites. There was high reliability for differentiating BP from non-BP subjects ($\kappa = 0.90$) and the BP diagnostic subtypes ($\kappa = 0.79$). For the non-mood disorders, κ s were ≥ 0.80 . The intraclass correlation coefficient was 0.96 for the KSADS-MRS and 0.98 for the KSADS Depression scale.

Global Impairment—The Children's Global Assessment Scale (C-GAS) was used to establish global level of functioning.³² The C-GAS is a clinician-rated global measure of impairment with excellent inter-rater reliability.³³ Scores range from 1-100 (scores over 70 indicate normal adjustment).

Familial Psychiatric Diagnosis—The primary caretaker of the subject was interviewed at intake about his/her personal psychiatric history using the Structured Clinical Interview for DSM-IV (SCID).³⁴ In addition, the primary caretaker was interviewed about the psychiatric status of the subject's first- and second-degree relatives using the Family History Screen (FHS).³⁵ For each disorder, the interviewer indicates which family members were reported as having experienced the disorder, separately for first- and second-degree relatives using a 4-point scale (1=not present, 2=possible, and 3=probable, 4=definite). The disorders examined in the current study were major depression, mania, anxiety disorders, ADHD, ODD, conduct disorder, schizophrenia, eating disorders, substance abuse, substance dependence, and suicidal attempts/completions. The FHS yields acceptable test-retest reliability and validity as determined by comparing informant family history diagnosis to best-estimate diagnoses based upon direct interview.³⁵

DSM-IV “Criterion A” Symptom Subgrouping

In order to further understand the clinical implications of the symptoms of irritability and elation in the diagnosis of BP, subjects were classified by primary DSM-IV criterion A manic symptoms. Independent of BP subtype, subjects were classified into one of three symptom subgroups using most serious lifetime manic episode scores on the MRS: (1) elation only, (2) irritability only, and (3) elation plus irritability. Subjects were classified as having elation or irritability if K-SADS MRS scores were rated in the “Mild but definite” range (a score of “3”) or above. All subjects met consensus criteria for BP based upon DSM-IV criteria. The subjects with mild category A symptoms still had other impairing symptoms above the clinical threshold and had clear episodicity.

Three hundred sixty-one of the total 446 subjects were classified into one of these three categories. Eighty-five subjects who were enrolled early in the study did not have most serious past episode of mania recorded using the K-SADS MRS so these subjects were not included in this analysis. The absence of data for these subjects was due to an early change in the COBY methodology (described above).

Statistical Analyses

SPSS[®] was used for data analysis. Differences in demographic, phenomenological, and family history factors among the three symptom groups were analyzed using analysis of variance, chi square, and non-parametric univariate tests (Kruskal-Wallis test), as required by the characteristics of the data. For comparing K-SADS Most Serious Lifetime Manic Symptoms, we conducted a multivariate analysis of covariance (MANCOVA) analysis in which age was covaried, since the groups were found to differ on this characteristic. In this MANCOVA, the elation and irritability scores that were used to define the groups were omitted. This analysis was used to determine that the groups differed with regard to Lifetime Symptoms overall. Because the MANCOVA analysis requires listwise case deletion, however, we also analyzed group differences on the K-SADS Lifetime Symptoms by univariate analysis of covariance, covarying for age. Since both methods yielded similar results, in Table 3 we report the univariate results since the Ns are higher for these analyses. All values are reported as means $\pm$ standard deviations unless otherwise specified. All p values are based on two-tailed tests with $\alpha = 0.05$.

Results

Analyses of Criterion A Symptoms

In order to describe the symptom stability of the three subgroups, we compared the elation and irritability MRS scores at the time of intake and at most serious past manic episode. As noted above, subjects did not need to meet criteria for a manic episode at intake to be enrolled in the

study. However, all subjects met threshold criteria for elation and/or irritability at intake or at most serious past episode. Sixty percent of the subjects met threshold criteria for elation and/or irritability at *both* intake and at the most serious past episode. Additionally, for the elation only group, 100% were below threshold criteria for irritability at both time points and similarly for the irritable only group, 100% were below threshold criteria for elation at both time points. Fifty-seven per cent of the Elation Only group ($n = 54$) met threshold criteria for high elation at intake and at most serious past episode. Sixty-one percent of the Irritability Only group ($n = 36$) met threshold criteria for high irritability at intake and at most serious past episode.

Demographics, bipolar subtype, duration of symptoms, and age of onset—As shown in Table 1, there were no significant differences between these three subgroups in terms of gender, race, living arrangements, SES or ethnicity. However, subjects with irritability only were significantly younger and had earlier pubertal status than subjects with elation only and subjects with both elation and irritability. There were no significant between-group differences in BP subtype, age of onset of mood symptoms, age of onset of BP, or duration of BP. There was a trend for the Irritability Only subjects to be more represented among those with BP-NOS. Subjects with elation plus irritability and elation only had significantly higher KSADS-MRS most serious lifetime mania compared to irritability only subgroups. In a secondary analysis, the specific MRS elation and irritability symptom scores were omitted from this recalculation and the results similarly indicated that the irritable only subjects had significantly lower total MRS scores than the other two groups $F(2,357)=5.5$, $p=.005$.

Comorbidity and lifetime phenomenological features—There were no significant differences between the symptom subgroups when comparing percent positive lifetime history of ADHD, ODD, Conduct Disorder, Substance Abuse, and anxiety disorders. There was also no effect of DSM-IV criterion A symptom profile on the lifetime presence of psychosis, suicidal ideation, suicide attempt, self injurious behavior, psychiatric hospitalizations, or exposure to psychopharmacological medication.

Family History—As shown in Table 2, after adjusting for the number of members within each family, there were no effects of DSM-IV criterion A symptom profile on rates of familial psychiatric illness in first degree relatives. This was also the case for second degree relatives, with the exception of depression and alcohol dependence. The irritability only subgroup had significantly more second degree family history of depression and alcohol dependence compared to the elation only subgroup. There was also a trend toward more second degree relatives with mania in the irritability-only group.

Mania Rating Scale Scores—As depicted in Table 3, there were many significant differences, after controlling for age and analyzed using MANCOVA, in mean K-SADS MRS for individual symptoms among the three symptom subgroups. The elation only and elation plus irritability subgroups had higher scores on the KSADS MRS items than the irritability only subgroup for the following symptoms: grandiosity, decreased need for sleep, increased goal directed activity, inappropriate laughing, and unusual energy. The elation plus irritability subgroup had significantly higher KSADS MRS scores than the irritability only group for increased creativity. The irritability only subgroup had significantly higher mood lability K-SADS MRS scores than the elation only and the elation plus irritability subgroups.

The frequency of grandiosity within each subgroup using the same cut-off scores (3 and above = present and 2 and below = not present) was analyzed. We found that 71% of the entire sample had mild or greater most serious lifetime grandiosity scores on the MRS while 74% of Elation Only, 56% of the Irritability Only, and 73% of Elation plus Irritability subjects had mild or above most serious lifetime grandiosity scores on the MRS. The three groups did not differ significantly on grandiosity score (chi square (2) = 5.324, $p = .07$).

We have also analyzed the sample using just the current (KSADS-MRS at intake) episode. There were no significant differences between the re-classified symptom subgroups when compared by bipolar sub-type, severity of disorder at baseline, percent co-morbid conditions, or family history in this analysis.

Discussion

The main goals of this study were to determine whether mania/hypomania in youth may be manifested with only irritability without elation and whether children with BP who have irritability and no elation differ on socio-demographic, phenomenological, and familial features from those who have elation and no irritability and from those who have both. We found that irritable only mania and elated only mania constituted 10% and 15% of the sample, respectively, with the majority having both elation and irritability. However, it is important to highlight that only the most severe lifetime manic episode symptoms that occurred at intake or in the past were analyzed. Thus, it is possible that the current grouping of “irritability only” bipolar children might have experienced an elated mania during another, though less severe, episode (and vice versa for the “elation only” bipolar children). Except for the irritable only subjects being significantly younger than the other two subgroups, there was no other between groups socio-demographic differences. There were also no significant between groups differences in the bipolar subtype, rate of psychiatric comorbidities, severity of illness, and duration of illness. Importantly, we found that the three subgroups, (irritability only, elation only, and elation plus irritability), did not differ with regard to family history of psychiatric disorders in first degree relatives. Rates of disorder in second degree relatives were also similar between the three subgroups with the exception of depression and alcohol abuse occurring more frequently in the irritability only subgroup. Taken together, these findings indicate that the DSM-IV A criteria is applicable to youth with bipolar disorder and that the irritability only subgroup, who in COBY also have distinct mood episodicity, is generally not significantly different from groups with elation, supporting continuing to consider irritability as a mood symptom in the diagnosis of juvenile bipolar disorder. These results also do not support prior research which suggests that irritability alone is the most common presentation of mania in children and adolescents.¹²

The presence of elation was associated with higher scores on most DSM-IV mania criterion B items. The elation only and elation plus irritability subgroups had higher individual scores on the KSADS MRS items than the irritability only subgroup. In this way, the elation subgroups appear similar to the “narrow” phenotype defined by Leibenluft and colleagues¹⁷ and also similar to the subjects included in Geller and colleagues' sample^{9,10} as well as that of Masi and colleagues.²¹ The irritability only subgroup appears to be most similar to the “intermediate phenotype” subjects also described by Leibenluft and colleagues.^{18,19} Over half (56%) of these irritable only subjects would have been included in Geller et al^{9,10} studies because of the presence of grandiosity. The irritability only subgroup defined in this study would not be considered similar to children referred to by Leibenluft and colleagues^{18,20,36} as “Severe Mood Dysregulation (SMD)” because SMD subjects by definition do not have mood episodes, but chronic symptoms, most fulfill the DSM-IV criteria for ODD/CD/ADHD, and do not fulfill the criteria for any DSM-IV BP subtype, including COBY's modification of the DSM-IV BP-NOS.^{23,24}

The finding that subjects with bipolar disorder who were in the irritable only subgroup did not differ from the two groups with elation in terms of frequency of family history of psychopathology is important. Brotman and colleagues reported that narrow phenotype bipolar disorder may be distinct from SMD in terms of familial aggregation of psychiatric illness.²¹ The fact that irritable-only subjects in COBY did not differ from subjects with elation may be explained by the necessity for mood episodicity in COBY's inclusion criteria. This emphasizes

the importance of considering episodicity when diagnosing youth with BP, particularly if they do not have elation.

We found that approximately 75 percent of the sample had both elation and irritability, while 15 percent had elation with no irritability and 10 percent were defined as having irritability without elation. These results suggest that irritability and elation most often co-occur which is consistent with other groups.^{10,11,21} It is also striking to note that the irritability alone group was significantly younger and that they had lower MRS scores on most items. These differing clinical presentations between children and adolescents may be attributable, at least in part, to the psychosocial and maturational changes that occur after puberty.³⁰ While speculative, it is possible that the younger age associated with the irritable only subgroup may be at least partially accounted for by their earlier developmental stage encompassing more predominant sub-cortical limbic mechanisms and less advanced prefrontal cortex operations in which mania is manifested by more diffuse irritability instead of elated mood which may require the acquisition of more complex neurodevelopmental processes.^{37,38} It will be of interest to see if these differences are just due to age and to see if this group will eventually begin to appear phenomenologically more similar to the other two groups or if they will remain different.

The results of the study must be considered in the context of certain limitations. The symptoms obtained from the most severe lifetime manic episode were subject to retrospective bias. Only the most severe lifetime manic episode symptoms were analyzed, thus missing possibly important retrospective clinical data from other episodes. Since COBY is following all subjects, longitudinal follow-up of this sample will more accurately account for all subsequent episodes of mood disturbance and evaluate the stability of the manic symptoms over time and whether more subjects present with only irritable mania. An additional limitation is that the family history method (FHS) used may underestimate the occurrence of disorders in relatives (especially second degree relatives) compared to direct interviews of family members. However, previous COBY studies have found that the FHS was able to discriminate clinical subgroups.^{39,40} Finally, the study sample was recruited by a variety of methods including referral from clinical programs. Therefore, the subjects may represent a more severely affected cohort of bipolar youth and thus results may not generalize to an epidemiological sample of bipolar youth. It could also be that the chance of referral would differ depending on irritability versus elation status. Finally, another limitation is that most of the sample was Caucasian, which may limit generalizability.

The results of this study support the DSM-IV A criteria for mania in youth. Our results also support previous findings that most youth with bipolar disorder have elation co-occurring with irritability with a small percentage, particularly in the younger children, having irritability only. The fact that the irritable only subgroup in this study has similar clinical characteristics and family histories of bipolar disorder, as compared to subgroups with predominant elation, provides support for continuing to consider irritability in the diagnosis of juvenile bipolar disorder, particularly if they have episodic illnesses and other DSM-IV category B symptomatology. Longitudinal follow-up of this sample will clarify whether the presence of predominance of elation or of irritability at baseline will be predictors of future clinical outcomes.

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References

1. Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR). American Psychiatric Association; 2000.
2. Biederman J, Wozniak J, Kiely K, et al. CBCL clinical scales discriminate prepubertal children with structured interview-derived diagnosis of mania from those with ADHD. *J Am Acad Child Adolesc Psychiatry* 1995;34:464–471. [PubMed: 7751260]
3. Biederman J. Mania is mistaken for ADHD in prepubertal children (Debate Forum: Affirmative). *J Am Acad Child Adolesc Psychiatry* 1998;37:1091–1093. [PubMed: 9785721]
4. Biederman J, Mick E, Spencer T, Wilens T, Faraone S. Therapeutic dilemmas in the pharmacotherapy of bipolar depression in the young. *J Child Adolesc Psychopharmacol* 2000;10:185–192. [PubMed: 11052408]
5. Biederman J, Faraone S, Wozniak J, Mick E, Kwon A, Aleardi M. Further evidence of unique developmental phenotypic correlates of pediatric bipolar disorder: Findings from a large sample of clinically referred pre-adolescent children assessed over the last 7 years. *J Affect Disord* 2004;82:S45–S58. [PubMed: 15571789]
6. Carlson G, Meyer S. Phenomenology and diagnosis of bipolar disorder in children, adolescents, and adults: complexities and developmental issues. *Development and psychopathology* 2006;18:939–969. [PubMed: 17064424]
7. Carlson G, Kelly K. Manic symptoms in psychiatrically hospitalized children-what do they mean? *J Affect Disord* 1998;51:123–135. [PubMed: 10743845]
8. Findling R, Gracious B, MaNamara N, et al. Rapid, continuous cycling and psychiatric comorbidity in pediatric bipolar I disorder. *Bipolar Disord* 2001;3:202–210. [PubMed: 11552959]
9. Geller B, Warner K, Williams M, Zimmerman B. Prepubertal and young adolescent bipolarity versus ADHD: assessment and validity using the WASH-U-KSADS, CBCL, and TRF. *J Affect Disord* 1998;51:93–100. [PubMed: 10743842]
10. Geller B, Zimmerman B, Williams M, et al. Diagnostic characteristics of 93 cases of prepubertal and early adolescent bipolar disorder phenotype by gender, puberty, and comorbid attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2000;10:157–164. [PubMed: 11052405]
11. Wozniak J, Biederman J, Kwon A, et al. How cardinal are cardinal symptoms in pediatric bipolar disorder? An examination of clinical correlates. *Biol Psychiatry* 2005;58:583–588. [PubMed: 16197929]
12. Wozniak J, Biederman J, Kiely K, Ablon J, Faraone S, Mundy E. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry* 1995;34:867–876. [PubMed: 7649957]
13. Pavuluri M, Birmaher B, Naylor M. Pediatric Bipolar Disorder: A Review of the last 10 Years. *J Am Acad Child and Adolesc Psychiatry* 2005;44:846–871. [PubMed: 16113615]
14. Strober M, Birmaher B, Ryan N, et al. Pediatric Bipolar Disease: current and future perspectives for study of its long-term course and treatment. *Bipolar Disord* 2006;8(4):311–321. [PubMed: 16879132]
15. Geller B, Craney J, Bolhofner K, Nickelsburg M, Williams M, Zimmerman B. Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar phenotype. *Am J Psychiatry* 2002;159:927–933. [PubMed: 12042179]
16. Kowatch R, Youngstrom E, Danielyan A, Findling R. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. *Bipolar Disord* 2005;7:483–496. [PubMed: 16403174]
17. Leibenluft E, Charney D, Towbin K, Bhangoo R, Pine D. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry* 2003;160:430–437. [PubMed: 12611821]
18. Leibenluft E, Blair J, Charney D, Pine D. Irritability in pediatric mania and other childhood psychopathology. *Ann NY Acad Sci* 2003;1008:201–218. [PubMed: 14998886]

19. Rich B, Schmajuk M, Perez-Edgar K, Fox N, Pine D, Leibenluft E. Different psychophysiological and behavioral responses elicited by frustration in pediatric bipolar disorder and severe mood dysregulation. *Am J Psychiatry* 2007;164:309–317. [PubMed: 17267795]
20. Brotman M, Kassem L, Reising M, Guyer A, Dickstein D, Rich B, Towbin K, Pine D, McMahon F, Leibenluft E. Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation. *Am J Psychiatry* 2007;164:1238–1241. [PubMed: 17671287]
21. Masi G, Perugi G, Toni C, Millepiedi S, Mucci M, Bertini N, Akiskal H. The clinical phenotypes of juvenile bipolar disorder: toward a validation of the episodic-chronic distinction. *Biol Psychiatry* 2006;59(7):603–610. [PubMed: 16487492]
22. National Institute of Mental Health research roundtable on prepubertal bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2001;40:871–878. [PubMed: 11501685]
23. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry* 2006;63:175–183. [PubMed: 16461861]
24. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry* 2006;63:1139–1148. [PubMed: 17015816]
25. Hollingshead, AB. Four-factor Index of Social Status. New Haven Connecticut: Yale University Sociology Department; 1975.
26. Peterson A, Crockett L, Richards M, Boxer A. A self-report measure of pubertal status: Reliability, validity, and initial norms. *J of Youth and Adolescence* 1988;17:117–133.
27. Marshall W, Tanner J. Variations in pattern of pubertal changes in boys. *Arch Dis Child* 1970;45:13–23. [PubMed: 5440182]
28. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-age Children- Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36:980–988. [PubMed: 9204677]
29. Puig-Antich, J.; Chambers, W.; Ryan, N. Schedule for affective disorders and schizophrenia for school-age children (6-18 years) Kiddie-SADS present episode (K-SADS-P), fourth working draft. Pittsburgh, PA: Western Psychiatric Institute and Clinic University of Pittsburgh School of Medicine; 1986.
30. Birmaher B, Axelson D, Strober M, Gill M, Yang M, Ryan N, Goldstein B, Hunt J, Esposito-Smythers C, Iyengar S, Goldstein T, Chiapetta L, Keller M, Leonard H. Comparison of manic and depressive symptoms between children and adolescents with bipolar spectrum disorders. *Bipolar Disorders* 2009;11:52–62. in press. [PubMed: 19133966]
31. Axelson D, Birmaher B, Brent D, et al. A preliminary study of the K-SADS Mania Rating Scale for children and adolescents. *J Child Adolesc Psychopharmacol* 2003;13:463–470. [PubMed: 14977459]
32. Shaffer D, Gould MS, Brasic J, et al. Children's Global Assessment Scale (C-GAS). *Arch Gen Psychiatry* 1983;40:1228–1231. [PubMed: 6639293]
33. Asarnow JR, Ben-Meir S. Children with schizophrenia and depressive disorders: A comparative study of premorbid adjustment, onset pattern and severity of impairment. *J Child Psych Psychiatry* 1988;29:477–488.
34. First, M.; Spitzer, R.; Williams, JB.; Gibbon, M. Structured Clinical Interview for DSM-IV SCID. Washington, DC: American Psychiatric Association; 1995.
35. Weissman M, Wickramaratne P, Adams P, Wolk S, Verdelli H, Olfson M. Brief screening for family psychiatric history: the family history screen. *Arch of Gen Psychiatry* 2000;57:675–682. [PubMed: 10891038]
36. Brotman M, Schmajuk M, Rich B, Dickstein D, Guyer A, Costello J, Egger H, Angold A, Pine D, Leibenluft E. Prevalence clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biological Psychiatry* 2006;60(9):991–997. [PubMed: 17056393]
37. Casey BJ, Jones RM, Hare TA. The adolescent brain. *Ann N Y Acad Sci* 2008;1124:111–126. [PubMed: 18400927]
38. Gogtay N, Giedd J, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A* 2004 May 25;101(21):8174–9. [PubMed: 15148381]

39. Rende R, Birmaher B, Axelson D, Strober M, et al. Childhood-onset bipolar disorder: Evidence for increased familial loading of psychiatric illness. *J Am Acad Child Adolesc Psychiatry* 2007 Feb; 46:197–204. [PubMed: 17242623]
40. Rende R, Birmaher B, Axelson D, Strober M, et al. Psychotic symptoms in pediatric bipolar disorder and family history of psychiatric illness. *J Affect Disord* 2006 Nov;96(1-2):127–31. [PubMed: 16814395]

Table 1

Total Sample Comparison by DSM-IV_Catgory A Most Severe Lifetime Mania Symptoms: Elation, Irritability, and Elation/Irritability

	All Subjects (N=361)	Elation Only (N=54)	Irritability Only (N=36)	Both Elation & Irritability (N=271)	Stat	Overall p-value
Demographics (% Yes or Mean ± SD)						
Age (years)	12.5±3.3	12.7±3.4 ^a	10.5±2.8 ^b	12.7±3.3 ^a	F _{2, 358} =6.8	0.01
Gender (% Male)	50.7	42.6	44.4	53.1	χ ² (3)=2.6	0.3
Race (% White)	79.5	72.2	88.9	79.7	χ ² (3)=3.7	0.2
Ethnic (% Hispanic)	6.6	7.4	2.8	7.0	FET	0.8
SES	3.4±1.2	3.6±1.2	3.1±1.2	3.3±1.2	F _{2, 358} =1.9	0.2
Living with both natural parents (% Yes)	40.7	37.0	41.7	41.3	χ ² (3)=0.4	0.8
Pubertal Status Category						
I	28.0	19.0	37.9	28.5	χ ² (6)=10.6	0.03
II-III	25.8	23.8	41.4	24.0		
IV-V	46.1	57.1 ^a	20.7 ^b	47.5 ^a		
Bipolar Category						
BPI	62.6	57.4	44.4	66.1	FET	0.1
BPII	5.5	5.6	8.3	5.2		
BPNOS	31.9	37.0	47.2	28.8		
Age of Onset/Duration of Illness						
Age of Onset of Mood Symptoms	8.2±4.2	8.3±4.4	6.8±3.4	8.4±4.2	KWχ ² (3)=3.6	0.2
Age of Onset of BP-Spectrum Illness (minimum 4)	9.2±4.0	9.6±4.3	8.2±3.3	9.2±4.0	KWχ ² (3)=2.3	0.3
Duration of BP-Spectrum Illness	3.3±2.6	3.1±2.6	2.4±1.7	3.4±2.7	F _{2, 358} =2.9	0.05
Symptom Severity-Most Severe Week During Month Prior to Intake						
MRS Score –Current	22.9±12.3	21.5±13.4	20.7±9.5	23.5±12.4	KWχ ² (3)=2.9	0.2
MRS Score- Most Serious Lifetime	33.8±8.3	30.9±8.2 ^a	28.5±7.6 ^a	35.1±8.0 ^b	F _{2, 356} =15.3	<0.001
DEP-P Score-Current	14.6±10.1	15.5±10.0	14.4±10.8	14.5±10.1	F _{2, 354} =0.2	0.8
DEP-P-Most Serious Lifetime	22.7±11.0	23.1±11.5	19.0±9.7	23.1±11.0	F _{2, 352} =2.3	0.10
Functional Impairment						
CGAS-Current	53.6±11.6	53.7±12.5	53.4±11.4	53.7±11.5	F _{2, 35} =0.01	1.0

	All Subjects (N=361)	Elation Only (N=54)	Irritability Only (N=36)	Both Elation & Irritability (N=271)	Stat	Overall p-value
CGAS Most Serious Lifetime	37.7±9.9	37.9±10.8	39.9±6.7	37.4±10.1 ^b	KW $\chi^2(3)=1.7$	0.4
Lifetime History of Comorbid Disorders (% Yes)						
Lifetime Any Anxiety D/O	39.1	35.2	36.1	40.2	$\chi^2(3)=0.6$	0.7
Lifetime Panic Disorder	4.4	1.9	5.6	4.8	FET	0.6
Lifetime SAD	24.1	20.4	22.2	25.1	$\chi^2(3)=0.6$	0.7
Lifetime Social Phobia	5.3	11.1	2.8	4.4	FET	0.1
Lifetime GAD	12.7	14.8	2.8	13.7	FET	0.1
Lifetime OCD	6.1	5.6	2.8	6.6	FET	0.8
Lifetime PTSD	6.6	1.9	11.1	7.0	FET	0.2
ADHD	60.7	59.3	69.4	59.8	$\chi^2(3)=1.3$	0.5
Conduct D/O	12.5	7.4	22.2	12.2	FET	0.1
ODD	38.0	35.2	25.0	40.2	$\chi^2(3)=3.3$	0.2
Substance/Alcohol, Abuse or Dependence	8.9	9.3	2.8	9.6	FET	0.4
Lifetime Phenomenological Features (% Yes)						
Psychosis	20.2	22.2	11.1	21.0	$\chi^2(3)=2.1$	0.4
Lifetime Major Depressive Episode	47.1	55.6	36.1	46.9	$\chi^2(3)=3.3$	0.2
Suicidal Ideation	75.1	75.9	77.8	74.5	$\chi^2(3)=0.2$	0.9
Suicidal Attempt	28.3	25.9	13.9	30.6	$\chi^2(3)=4.6$	0.1
Self-Injurious Behavior	41.7	44.4	38.9	41.5	$\chi^2(3)=0.3$	0.9
Psychiatric Hospitalization	47.8	48.1	38.9	48.9	$\chi^2(3)=1.3$	0.5
Psychotropic Medication	94.5	92.6	94.4	94.8	FET	0.7
Medication	97.2	98.1	94.4	97.4	FET	0.5

Age of Onset of BP-Spectrum Illness is set age 4 as the minimum.

Lifetime Anxiety includes Panic Disorder, Separation Anxiety Disorder (SAD), Social Phobia, Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD) and Post-Traumatic Stress Disorder (PTSD).

Values with different superscripts are significant at $p \leq 0.05$

FET= Fisher's Exact Test

KW = Kruskal-Wallis Test

BP1= Bipolar 1 Disorder (as defined by the DSM-IV-TR)
 BP2= Bipolar 2 Disorder (as defined by the DSM-IV-TR)
 BPNOS=Bipolar NOS Disorder (as defined by the COBY study noted in the body of the text)
 SES= Socio-Economic Status
 MRS=Mania Rating Scale of the KSADS-PL (Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version)
 DEP-P=Depression Section of the KSADS-PL (Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version)
 C-GAS=Children's Global Assessment Scale
 D/O= Disorder
 ODD= Oppositional Defiant Disorder

Table 2

Comparison of Family History by DSM-IV Category A Most Severe Lifetime Mania Symptoms: Elation, Irritability, and Elation/Irritability

	All Subjects (N=361)	Elation Only (N=54)	Irritability Only (N=36)	Both Elation & Irritability (N=271)	Stat	Overall p-value
Any 1st Family History with lifetime Disorder (% Yes)						
Depression	75.7	80.4	69.7	75.5	$\chi^2(3)=1.3$	0.5
Mania/Hypomania	38.6	29.4	34.4	41.0	$\chi^2(3)=2.7$	0.3
ADHD	35.6	38.0	40.6	34.4	$\chi^2(3)=0.9$	0.6
Conduct D/O	23.3	24.0	21.9	23.3	$\chi^2(3)=0.04$	1.0
Schizophrenia	1.2	2.0	0.0	1.2	$\chi^2(3)=1.0$	0.6
Anxiety	55.6	54.9	50.0	56.5	$\chi^2(3)=0.4$	0.8
Substance/Alcohol Abuse	31.9	31.4	21.2	33.5	$\chi^2(3)=2.1$	0.4
Substance/Alcohol Dependence	33.4	25.5	47.1	33.2	$\chi^2(3)=4.3$	0.1
Suicidal Attempt or Completion	23.7	25.5	21.2	23.7	$\chi^2(3)=0.2$	0.9
Any 2nd Family History with lifetime Disorder (% Yes)						
Depression	69.9	62.0 ^a	87.1 ^b	69.4 ^a	$\chi^2(3)=6.5$	0.04
Mania/Hypomania	38.6	26.0 ^a	48.4 ^b	39.9 ^b	$\chi^2(3)=5.4$	0.07
ADHD	31.5	26.5	32.3	32.4	$\chi^2(3)=0.8$	0.7
Conduct D/O	26.5	28.6	25.8	26.1	$\chi^2(3)=0.1$	1.0
Schizophrenia	5.6	6.0	3.2	5.8	$\chi^2(3)=0.6$	0.7
Anxiety	49.1	56.0	58.1	46.5	$\chi^2(3)=2.4$	0.3
Substance/Alcohol Abuse	47.7	46.0	45.2	48.4	$\chi^2(3)=0.4$	0.8
Substance/Alcohol Dependence	46.6	34.0 ^a	67.7 ^b	46.6 ^a	$\chi^2(3)=9.0$	0.01
Suicidal Attempt or Completion	32.0	30.0	38.7	31.6	$\chi^2(3)=0.7$	0.8

Values with different superscripts are significant at $p \leq 0.05$

Controlling for the number of relatives

Table 3

Comparison of K-SADS Most Serious Lifetime Manic Symptoms by DSM-IV Category A Mania Symptoms: Elation, Irritability, and Elation/Irritability

	All Subjects (N=361)	Elation Only (N=54)	Irritability Only (N=36)	Both Elation & Irritability (N=271)	Stat	Overall p-value
Grandiosity	3.3±1.4	3.5±1.5 ^a	2.6±1.4 ^b	3.3±1.4 ^a	F=3.5 (2, 359)	0.03
Decreased need for sleep	4.0±1.9	4.6±1.6 ^a	2.8±1.9 ^b	4.0±1.8 ^a	F=9.0 (2, 358)	<0.0001
Accelerated Speech,	4.1±1.2	4.0±1.4	3.6±1.3	4.2±1.1	F=2.2 (2, 359)	0.11
Racing thoughts	3.4±1.6	3.5±1.6	2.7±1.6	3.7±1.6	F=2.0 (2, 358)	0.14
Flight of ideas	3.5±1.4	3.1±1.5 ^a	2.8±1.5 ^a	3.7±1.3 ^b	F=9.7 (2, 354)	<0.0001
Distractibility	3.5±1.1	3.4±1.2	3.4±1.2	3.5±1.1	F=0.5 (2, 358)	0.6
Increased Goal-directed Activity	3.0±1.6	3.4±1.7 ^a	2.1±1.3 ^b	3.1±1.5 ^a	F=4.86 (2, 358)	0.01
Motor Hyperactivity	4.3±1.1	4.2±1.3	4.1±1.2	4.4±1.1	F=1.4 (2, 355)	0.3
Poor Judgment	3.9±1.6	3.4±1.7 ^a	3.9±1.5 ^b	3.9±1.5 ^b	F=3.0 (2, 359)	0.05
Unusual Energy	4.5±1.3	4.7±1.3 ^a	3.8±1.7 ^b	4.6±1.2 ^a	F=3.8 (2, 358)	0.02
Hallucinations	1.8±1.3	1.8±1.4	1.5±0.9	1.9±1.4	F=1.5 (2, 356)	0.2
Delusions	1.4±0.9	1.5±1.1	1.1±0.4	1.4±1.0	F=.98 (2, 352)	0.4
Mood Lability	4.1±1.1	3.4±1.3 ^a	4.6±1.0 ^b	4.2±1.0 ^c	F=13.39 (2, 353)	<0.0001
Inappropriate Laughing	2.8±1.1	2.9±1.0 ^a	2.3±1.2 ^b	2.9±1.0 ^a	F=4.9(2, 357)	0.001
Uninhibited People Seeking	2.5±1.2	2.4±1.1	2.2±1.1	2.5±1.2	F=0.66 (2, 357)	0.5
Increased Productivity	2.2±1.2	2.5±1.2	1.9±1.0	2.3±1.2	F=1.8 (2, 358)	0.2
Sharpened Creative Thinking	2.3±1.1	2.3±1.1	1.8±1.0	2.3±1.1	F=2.2 (2, 353)	0.1

	All Subjects (N=361)	Elation Only (N=54)	Irritability Only (N=36)	Both Elation & Irritability (N=271)	Stat	Overall p-value
Hyper Sexuality	2.3±1.2	2.1±1.1	2.3±1.2	2.3±1.3	F=0.6 (2, 356)	0.5
Sentence Incoherence	1.7±1.1	1.4±1.0	1.7±1.1	1.7±1.2	F=1.2 (2, 357)	0.3
Derailment	1.5±1.0	1.5±1.0	1.6±1.1	1.6±1.1	F=0.3 (2, 356)	0.7

Values with different superscripts are significant at $p \leq 0.05$

Multivariate Analysis-MANCOVA (controlling for Age)

KSADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version