How Cardinal are Cardinal Symptoms in Pediatric Bipolar Disorder? An Examination of Clinical Correlates

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Background: *The main goal of this study was to test whether the hypothesized cardinal symptom of euphoria results in differences in clinical correlates in bipolar youth ascertained with no a priori assumptions about cardinal symptoms.*

Methods: *Subjects (n = 86) satisfying DSM-IV criteria for bipolar disorder with and without the proposed cardinal symptom of euphoria were compared in their bipolar symptom pattern, functioning and patterns of comorbidity.*

Results: *Among Criterion A (abnormal mood), we found that severe irritability was the predominant abnormal mood rather than euphoria (94% vs. 51%). We also found that among Criterion B items, grandiosity was not uniquely overrepresented in youth with mania, nor did the rate of grandiosity differ whether irritability or irritability and euphoria were the Criterion A mood symptom. Neither symptom profile, patterns of comorbidity nor measures of functioning differed related to the presence or absence of euphoria.*

Conclusions: *These findings challenge the notion that euphoria represents a cardinal symptom of mania in children. Instead they support the clinical relevance of severe irritability as the most common presentation of mania in the young. They also support the use of unmodified DSM-IV criteria in establishing the diagnosis of mania in pediatric populations.*

Key Words: Pediatric, children, bipolar, mania, euphoria, irritability

Converging evidence from multiple laboratories supports the notion that pediatric bipolar disorder (BPD) is a common, highly morbid pediatric psychiatric disorder (Biederman et al 2004; Carlson and Kelly 1998; Faedda et al 2004; Findling et al 2001; Geller et al 2000, 2001, 2004; Leibenluft et al 2003; Strober et al 1995; Wozniak et al 1995). While children with BPD are diagnosed in accordance with the DSM-IV diagnostic criteria, uncertainties remain as to whether certain features of the disorder in youth are fundamentally important in confirming the diagnosis.

Some investigators (Geller et al 2000, 2002a, 2002b; Leibenluft et al 2003) have argued that because euphoria (as opposed to irritability) is unique to bipolar disorder, it should be considered the defining mood disturbance of bipolar children. Although both Geller et al (2000) and Liebenluft et al (2002a, 2002b) argued that grandiosity also is a hallmark symptom of pediatric bipolar disorder, this represents a significant departure from the DSM-IV criteria for mania in which grandiosity is listed as one of seven possible criterion B symptoms. Moreover, research based on these assumptions that used samples selected by the presence of euphoria (and/or grandiosity) is compounded by the circularity of the research design in which the independent variable is also used as the outcome variable. Thus, more research is needed to clarify the main features of pediatric bipolar disorder using samples unselected by the hypothesized "cardinal" features.

Although irritability is a bona fide mood criterion for bipolar disorder in DSM-IV, because it is also included in the defining features of other psychiatric disorders such as depression and oppositional defiant disorder, it has been criticized as nonspecific. While it is true that irritability can occur in various psychiatric conditions, the type of irritability observed in children with mania is extremely severe and arguably distinct from other forms of irritability seen in other psychiatric conditions. Therefore, the severe form of irritability seen in children with bipolar disorder can be considered as an equally meaningful mood criterion for pediatric mania (Mick et al 2005) as that of euphoria. Furthermore, irritability may be the most common abnormal mood associated with pediatric bipolar disorder (Wozniak 2003; Wozniak et al 1995, 2001) and the one that commonly drives the clinical referral.

The purpose of this study was to empirically test the heuristic utility of the hypothesized cardinal feature of euphoria in pediatric bipolar disorder. To this end we studied a large sample of youth with DSM-IV bipolar disorder ascertained without any preconceived notion as to which DSM-IV features are 'cardinal.' Subjects with and without euphoria were compared in their clinical correlates including symptom pattern, functioning and patterns of comorbidity. Based on the literature and prior work, we hypothesized that the proposed cardinal feature will not be fundamentally important in the diagnosis of pediatric bipolar disorder. We also hypothesized that irritability would be the most common aberrant mood in this population. To our knowledge, this is the first attempt at testing the utility of cardinal symptoms in a sample of bipolar children and adolescents ascertained according to DSM-IV criteria, endorsing either severe irritability or euphoria or both.

Methods and Materials

Subjects were youth (≤18 years) with DSM-IV BPD on structured diagnostic interview and confirmed by clinical interview, who had been consecutively referred to a family study of pediatric bipolar disorder from ascertained outpatients from our Pediatric Psychopharmacology Clinic at Massachusetts General Hospital (MGH). Thus, parents calling for a psychiatric evaluation of their child were told about the family genetic study of pediatric bipolar disorder. Those interested who also met inclusion and exclusion criteria signed informed consent and participated in the study. Children and adolescents male and female aged 4-17 were included if they met DSM-IV criteria for bipolar I disorder, and their first degree relatives were available for

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study. Potential probands were excluded if they had major sensorimotor handicaps (deafness, blindness), psychosis due to schizophrenia, severe autism, inadequate command of the English language, or a Full Scale IQ less than 80. No ethnic, racial or gender group was excluded from the study. Subjects met criteria for bipolar disorder I according to DSM-IV criteria, endorsing either severe irritability or euphoria, or both ($n = 86$). We stratified our analyses according to the presence of euphoria. This study was reviewed and approved by the MGH human subjects committee and all subjects gave informed consent or assent, in the case of those under age 18.

For the first step of the ascertainment procedure, a trained research assistant conducted a phone screen reviewing symptoms of DSM-IV bipolar disorder. Next, a research assistant administered the structured psychiatric interview and, by our diagnostic procedure, we determined which diagnostic criteria were met. Prior to reviewing the structured interview results, the principal investigator (PI) conducted a clinical interview of each proband with his or her parent(s) to confirm the clinical diagnosis of bipolar disorder and to administer the Young Mania Rating Scale (YMRS). High concordance between clinical interview and trained rater interview was documented (Wozniak et al 2003).

Structured interviews of all youth were performed using the Schedule for Affective Disorder and Schizophrenia for School-Aged Children, Epidemiologic Version (K-SADS-E) (Orvaschel 1994) by highly trained and supervised raters who were blind to the subject's clinical diagnosis apart from their knowledge of the subject's referral to a child psychiatry clinic. All raters held either bachelor's or master's degrees in psychology and were supervised by the senior investigator (JW). These raters conducted indirect interviews with a parent, usually the mother, for all children, and direct interviews with children and adolescents aged 12 and older. In addition, all index subjects/proband youth were directly interviewed with clinical interview by the PI (JW). Diagnostic assessments of adults (first-degree relatives) were based on direct interviews using the Structured Clinical Interview for DSM-IV (SCID) (First et al 1997) supplemented with K-SADS-E modules to cover childhood diagnoses.

All diagnoses were reviewed blindly by a diagnostic sign-off committee of board-certified child and adult psychiatrists and licensed Ph.D. psychologists, chaired by a senior investigator (JB). The committee reviewed the items endorsed during the interview with detailed notes taken by the interviewer. Diagnoses presented for review were considered positive only if a consensus was achieved that criteria were met to a degree that would be considered clinically meaningful. By "clinically meaningful," we mean that the data collected from the structured interview indicated the diagnosis should be a clinical concern due to the quality and severity of symptoms, the associated impairment, and the coherence of the clinical picture. A key point is that these diagnoses are made as part of the clinical assessment procedures for our clinic; they were not simply research diagnoses computed by counting symptoms endorsed, and applying an algorithm. We consider these diagnoses "clinically meaningful" because they are routinely used in planning the treatment of children in our clinic. We computed kappa coefficients of agreement by having three experienced, board-certified child and adult psychiatrists diagnose subjects from audio taped interviews made by the assessment staff. Based on 175 interviews done in our research settings for a variety of studies using the same methodology, all disorders achieved kappas higher than .82. The mean kappa was .90. We attained a kappa of 1.0 for attention deficit hyperactivity disorder (ADHD) and .91 for BPD. The reliability of maternal reports of these disorders over a one-year period was also high, with kappas for ADHD and BPD being .95 and .71 (Faraone et al 1995).

For every diagnosis, information was gathered about the ages at onset and offset of symptoms, number of episodes, and treatment history. Since the anxiety disorders comprise many syndromes with a wide range of severity, we use two or more anxiety disorders as a summary variable, and refer to this as "multiple anxiety disorders" (Biederman 1990).

To be given the lifetime diagnosis of BPD, the child had to meet full DSM-IV criteria for a manic episode with associated impairment. Thus, a child must have met criterion A for a period (one week or longer) of extreme and persistently elevated, expansive or irritable mood, plus criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance, plus criterion C, associated impairment. The approach taken by the K-SADS to evaluate BPD criteria is similar to that taken by the original SADS. First, a period of time characterized by the mood features in section A are established. According to the K-SADS, we ask about euphoria in the mania section in the following manner: Has there been a period of a week or longer when (child's name) felt really, really good, almost too good, like (s)he's on top of the world, where you or other people might have been concerned about (child's name)? According to the KSADS we ask about irritability in the mania section in the following manner: Has there been a time for a week or longer when (child's name) felt super angry, grouchy, cranky or irritable all the time? So much so that (child's name) might be explosive or start fights with random people? Then each of the criteria in B are addressed. For example, to assess B1 in the mania module the interviewer would ask the parent: During this period did (child's name) feel especially self-confident? . . . like he/she could do anything? . . . was special? . . . in what way? . . . special powers? . . . stronger? . . . smarter?

In addressing the course of mania, we utilized information on subjects' onset and offset ages, to determine the duration of the disorder, combined with their reported number of lifetime episodes, to yield a categorical description of their manic experience as being either chronic or episodic. A chronic course was defined by those subjects who reported rapid cycling (more than four episodes per year), multiple episodes each lasting (on average) at least 12 months or more, or a single episode lasting more than 12 months. Rapid cyclers were further categorized as having ultra-rapid cycling (more than 20 episodes in a year) or ultradian cycling (more than 300 episodes in a year). Episodicity encompassed those subjects who reported multiple episodes each lasting (on average) less than 12 months in duration or a single episode lasting less than 12 months.

Psychosocial functioning was assessed using the Global Assessment of Functioning Scale (GAF: 0 (worst) to 90 (best)) (Endicott et al 1976). Socioeconomic status (SES) was measured using the Hollingshead Four-Factor Index, with lower scores indicating higher SES (Hollingshead 1975).

Data are expressed as frequencies (percents) or means ± standard deviations. Continuous data were analyzed by two-sample *t*-tests or one-way analyses of variance (ANOVAs) and categorical data by chi-square analysis or Fisher's exact test. Because our hypotheses predict few differences between groups, we decided not to make any adjustments for multiple comparisons as that leads to a more conservative test of our hypotheses. By taking this approach of a liberal, unadjusted definition of statistical significance, if we fail to find differences between the groups, then findings actually provide stronger

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