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Pediatric bipolar disorder: evidence for prodromal states and early markers

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Abstract

Background—Childhood bipolar disorder remains a controversial but increasingly diagnosed disorder that is associated with significant impairment, chronic course and treatment resistance. Therefore, the search for prodromes or early markers of risk for later childhood bipolar disorder may be of great importance for prevention and/or early identification.

Methods—Literature searches were conducted to identify reviews, case reports and empirical papers addressing the issue of prodromes of childhood bipolar disorder.

Results—A total of 54 articles were found that related to bipolar prodromes, risk factors for later childhood bipolar disorder, childhood risk for adult bipolar disorder, mania manifestations in early childhood, and neuropsychological and biological markers of childhood bipolar disorder. A review of articles suggest (a) childhood bipolar prodromes may be detectable prior to the onset of the disorder, (b) prodromal symptoms may display episodicity during childhood, (c) there is evidence of possible endophenotypic markers such as deficits in executive function, sustained attention, and emotion labeling, (d) there is a potential association with functional, structural, and biochemical alterations evident in brain structures involved in mood regulation, (e) a link between childhood bipolar disorder with early temperamental markers, such as emotional regulation and behavioral disinhibition and (f) there is some early but promising evidence of effective psychotherapeutic preventions.

Conclusions—There has been very limited investigation of early prodromes of childhood bipolar disorder. Based on the promising findings of prodromes as well as high-risk states and possible endophenotypic markers, more controlled and targeted investigations into the early markers of bipolar disorder appear warranted and potentially fruitful. Until such longitudinal studies with appropriate controls are conducted, specific markers for bipolar prodromes will remain elusive, although evidence suggests they are manifest in at least some subgroups. The finding of promising psychotherapeutic prevention programs underscores the need to find specific and sensitive markers of bipolar prodromes in childhood.

Keywords

Childhood bipolar disorder; prodromes

Over the past decade, there has been a great deal of public health controversy about childhood bipolar disorder (National Institute of Mental Health research roundtable on prepubertal bipolar disorder, 2001). The diagnosis of this disorder, previously virtually unrecognized in children, has increased exponentially in community mental health settings

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over the past several years (Moreno et al., 2007). At the same time, there remains considerable lack of consensus about the age-adjusted criteria that should be used for diagnosis in children. Effective treatments for the childhood disorder remain even more unclear. However, some areas of agreement have been established, despite the controversy, based on converging findings from numerous independent research groups describing a pediatric bipolar syndrome characterized by minor adjustments to the standard DSM-IV criteria (Axelson et al., 2006; Biederman et al., 2005; Geller, Tillman, Craney, & Bolhofner, 2004). Further, several independent research groups have also provided longitudinal data demonstrating that pediatric bipolar disorder is a chronic remitting and relapsing condition, with one study showing continuity into early adulthood (Birmaher et al., 2009, 2006; DelBello, Hanseman, Adler, Fleck, & Strakowski, 2007; Geller, Tillman, Bolhofner, & Zimmerman, 2008). Numerous studies have established that across a range of phenotypes described, pediatric bipolar disorder is a severe and impairing disorder with relative treatment resistance (for review see Kowatch & DelBello, 2006). Based on these findings, the search for an identifiable prodrome, or early markers of risk for later childhood bipolar disorder, is of great potential public health importance. If a clear and valid prodrome could be identified, it could facilitate earlier and potentially more effective intervention before development of the full and highly impairing clinical syndrome.

An issue pertinent to the identification of a bipolar prodrome is the clarification of which symptoms are the most sensitive and specific markers of the clinical disorder and therefore deemed the 'cardinal symptoms' of bipolar disorder (BPD). The definitive clarification of the cardinal symptoms of bipolar disorder, as distinct from disruptive behavioral disorders or attention deficit hyperactivity disorder (ADHD), remains to be determined. However, Geller et al. (2002) have attempted to inform this question in an investigation of the phenomenology of childhood bipolar disorder by comparing the clinical characteristics of children meeting criteria for BP-I to those without BP-I but with ADHD. Grandiosity and elation emerged as highly specific symptoms of BP-I not found in ADHD. These conclusions, however, remain controversial, thus the symptoms of elation and grandiosity have not been accepted as cardinal symptoms by some research groups.

The age-adjusted developmental manifestations of mania symptoms in childhood, in contrast to developmental norms, have been described in detail by Geller et al. (2002). One issue in the identification of these symptoms in children is the challenging distinction between clinical grandiosity and elation, for example, and fantasy play about grand powers and joyful exuberance arising normatively during this developmental period. For this reason, intensity, impairment, and lack of contextual appropriateness are used to distinguish clinical symptoms from normative extremes. Along this line, an interesting question is whether prodromal manifestations of such symptoms might not appear out of the range of normative extremes and may be characterized by a child who is unusually confident or controlling or a child who is unusually joyful and silly. Such characteristics may be of interest as potential prodromes, especially when they occur episodically or show fluctuation. However, it should be noted that the question of episodicity of mania symptoms in childhood BPD is highly controversial, with many groups reporting very rapid ultradian cycling. Also notable is that varying definitions of cycles and episodes have been used, further complicating the issue (Findling et al., 2001; Geller et al., 2002; Tillman & Geller, 2003; Wozniak et al., 2005). When such characteristics intensify and cross the clinical threshold or become associated with later social and clinical impairment they are of obvious interest as clinical markers. While differences in the manifestations or frequency of these symptoms as a function of gender, culture, and socioeconomic status are possible and potentially important, this area remains empirically unexplored to date. There are several comprehensive diagnostic interviews in addition to more streamlined mania rating scales now available, designed to assess the age-appropriate manifestations of mania symptoms, such as the WASH U K-

SADS (Geller, William, Zimmerman, & Frazier, 1996), the Kiddie Mania Rating Scale (K-MRS; Axelson et al., 2003) and the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978), that are commonly used in bipolar research.

A prodrome, defined by symptom manifestations or early markers or signs prior to the onset of a disorder, represents a more optimal point of intervention in a difficult to treat disorder. Several lines of investigation have been used in attempts to identify prodromes in Axis I psychiatric disorders. The most fruitful line of evidence thus far has been provided by studies in which individuals at very high risk for having a disorder are followed prospectively (Egeland et al., 2003; Shaw, Egeland, Endicott, Allen, & Hostetter, 2005). Related to these investigations is the identification of early and milder symptom manifestations that may be markers of a later bipolar disorder. These may be either symptoms of mania that arise at a low intensity and therefore remain sub-clinical or one or more manic symptoms such as grandiosity or elation as described above at the clinical level without other key symptoms present to meet full criteria for the disorder.

Another less direct line of evidence focuses on the search for endophenotypes, or heritable biomarkers. Endophenotypes have been one focus of inquiry yielding some interesting results related to investigations of prodromes in schizophrenia (Cornblatt et al., 2003; Lencz, Smith, Auther, Correll, & Cornblatt, 2003). In such studies, endophenotypes may help identify individuals likely to manifest prodromal states. In examining high-risk patients, these studies have highlighted the conceptualization of schizophrenia within a neurodevelopmental context, the quantification of multiple dimensions of prodromal symptomatology and cutoff points for defining health and illness. Cornblatt et al. (2003) assert that an overly narrow definition of the prodrome can be detrimental, leading to potentially effective interventions being overlooked. However, to date, despite interest and some findings in the areas of attention and facial affect processing (reviewed below), there are few promising findings leading to a robust or specific endophenotype for bipolar disorder in either the child or adult literature.

The question of whether early onset depressive symptoms or clinical depression may be a marker or prodrome of later bipolar disorder has also been of interest. Numerous investigations have demonstrated high rates of switching to mania among depressed children (reviewed below). Alternatively, disruptive symptoms not specific to bipolar disorder per se (but often observed in bipolar subjects) have been identified that appear to be associated with the later onset of bipolar disorder. High-risk designs in which the offspring of bipolar parents are studied have also been informative. This population has been identified as developing early onset bipolar spectrum disorders at significantly higher rates than other psychiatric disorders (Birmaher et al., 2009). The notion that family history of bipolar disorder can be used as a marker of risk, to identify populations in which increased vigilance for symptoms or prodromes is advised, has been widely accepted in clinical practice. These lines of investigation will be reviewed in this paper.

As mentioned above, when evaluating the prodromal symptoms of bipolar disorder it is important to understand and interpret these symptoms in the contexts in which they have developed. Contextual effects include the impact of developmental level, gender, SES, race, and culture on symptom presentation. However, research in this area is sparse and has largely been limited to the adult population. When examining the effects of race and culture in bipolar children and adolescents, evidence that African-American bipolar youth are more likely than Caucasians to be diagnosed as having psychotic features has been provided (Axelson et al., 2006). This finding could represent a true cultural difference or rather a bias on the part of clinicians. In examining populations outside of the US, the results are varied. A study on the diagnosis of bipolar disorder in children and adolescents conducted in

Germany concluded that bipolar disorder is less likely to be diagnosed in Germany compared to the US (Meyer, Koßmann-Böhm, & Schlottke, 2004). However, a study from Brazil on juvenile bipolar disorder showed similar patterns of prevalence and clinical presentation when compared to results from research investigations in the US and Canada (Tramontina, Schmitz, Polanczyk, & Rohde, 2003). It is evident that the existing research on contextual effects on bipolar symptomatology in children is inconclusive and may be highly related to bias or trends in clinical perspective and thus warrants further research in this area.

The hypothesis that an identifiable bipolar prodrome can be detected months or years prior to the onset of the first episode of an Axis I bipolar disorder in childhood has been supported by some available longitudinal data. In keeping with these findings (described in detail below), epidemiological data has suggested that symptoms of bipolar disorder were evident prior to the age of 15 in a sample of bipolar adults based on retrospective reports (Lewis, 2001). Data from an Amish population suggest that prodromal affective symptoms as well as 'mini clusters' of symptoms that have a cyclical manifestation can be identified during childhood and as early as 9–12 years prior to the onset of the full clinical disorder during adulthood (Egeland et al., 2003; Shaw et al., 2005). These intriguing findings suggest that the search for a prodrome for bipolar disorder is worthwhile and should be pursued on a larger scale with well-controlled design strategies.

Methods

PubMed, MEDLINE, and PsychINFO literature searches were used to identify reviews and empirical papers addressing the issue of prodromes of childhood bipolar disorder. Owing to the paucity of research in this area, the inclusion criteria were expanded to include any article focused on the topic of bipolar prodromes as well as related case reports. A number of papers that addressed the topic of prodromes or risk factors pertinent to childhood bipolar disorder in general were found. Additional papers were located using these sources, resulting in a total of 10 papers. Subsequently, a hand search of papers investigating risk factors for later childhood bipolar disorder and childhood risk for adult bipolar disorder was also undertaken and additional relevant papers were found. This search resulted in 17 papers that were reviewed. In addition, papers were reviewed on topics which had potential relevance to the subject matter of bipolar prodromes. These topics included: neuropsychological markers of childhood bipolar disorder (7), biological markers of childhood bipolar disorder (10), mania manifestations in early childhood (6) and treatment approaches (4). In summary, there were 54 articles found that related to bipolar prodromes, risk factors for later childhood bipolar disorder, childhood risk for adult bipolar disorder and other relevant topics. These articles comprised case reports (2), literature reviews (10), and empirical research (42). The characteristics of the articles on empirical research directly related to prodromes and risk factors in childhood bipolar disorder are summarized in Table 1.

Results

Direct investigations of mania prodromes in childhood: retrospective and prospective studies

In an investigation of bipolar prodromes in children and adolescents, Correll et al. (2007) conducted structured retrospective interviews, designed to assess for prodromal symptoms, with the caregivers of individuals with childhood and adolescent onset bipolar disorder. To improve the reliability of such retrospective reports, subjects who could be captured in close proximity to their first manic episode were selected. While an exact interval between first episode and interview was not specifically defined, this study focused on children and adolescents who had their first episode within the past 5 years. A lengthy mania prodrome

with predominantly slow onset was identified that was characterized by sub-threshold depressive and mania symptoms as well as symptoms of more general psychopathology. In a further study of 52 youth with newly emerging and moderately severe mania (onset before 19 years of age), prodromal symptoms were assessed and compared to those known in subjects with psychotic mania or schizophrenia. Investigators reported that an insidious prodromal state lasting >1 year was evident in 52% of bipolar subjects and a sub-acute (1–12 months) prodromal state was detected in 44%. In contrast, acute onset of mania appeared as a rare phenomenon and was reported in only 4% of subjects. While there was some overlap between symptoms prodromal to mania and schizophrenia, the following key symptoms were found more frequently in mania: difficulty thinking, depressed mood and mood lability, decreased concentration, and agitation. This investigation suggests that a relatively long mania prodrome is detectable in childhood, opening an opportunity to target these symptoms for early intervention/prevention in adolescent bipolar disorder.

Providing support for prodromal signs and symptoms similar to those described by Correll et al. (2007), retrospective reports from a sample of $N = 58$ Amish bipolar subjects revealed that early mood, sleep, and psychomotor alterations during childhood were salient symptoms observed prior to the onset of full bipolar disorder (Egeland, Hostetter, Pauls, & Sussex, 2000). These compelling retrospective reports document early insomnia, bold, bossy, and grandiose-like behaviors early in childhood as well as mood lability, depressed mood, and vegetative signs in individuals who later developed bipolar disorder. These retrospective reports were strikingly similar to those previously described by Lish, Dime-Meenan, Whybrow, Price, and Hirschfeld (1994) based on retrospective recollections of childhood symptoms in bipolar adults. However, these data from the Amish sample are strengthened by the fact that they were obtained at first hospitalization prior to diagnosis, a design feature that reduces or eliminates the possible recall bias inherent in recollected reports of already diagnosed adults who are familiar with the experiences and significance of manic symptoms. Of note was that many of these symptoms arose as many as 9 years prior to the onset of the clinical syndrome, further supporting the idea that prodromal mania symptoms may be detectable many years before the onset of bipolar illness. Duffy, Alda, Hajek, Sherry and Grof (2009) observed a similar pattern of symptoms when assessing high-risk offspring of bipolar parents. Specifically, their data suggested the emergence of a developmental trajectory beginning with non-mood antecedents (sleep and anxiety) in childhood, minor mood symptoms post-puberty and major mood symptoms in late adolescence.

A prospective study in an Amish population was also undertaken to investigate bipolar prodromes in healthy children at high risk for the disorder compared to low-risk controls (Egeland et al., 2003). This population was of interest and highly feasible for such an undertaking based on the known high genetic loading for bipolar disorder, the presence of large sibships, stability of family life, and geographic immobility in Amish communities. In this unique study, children of bipolar parents and children of parents without psychiatric disorders were studied annually for 7 years. Histories of child behaviors were obtained and randomized. Subjects were subsequently rated for risk for bipolarity by clinicians blind to family history status. Children of bipolar parents were rated as high risk significantly more frequently than children from families without bipolar illness. Among a variety of clinical features found to be related to high risk status were mood lability, anxiety, being easily excited, somatic complaints, and appearing stubborn or determined. Further, mini clusters of these symptoms were found, suggesting that the natural history of the development of the disorder may be preceded by episodic prodromal features. A subsequent 10-year follow-up of this sample revealed 5 additional prodromal markers: high energy, decreased sleep, problems with thinking and concentration, and excessive loud talking (Shaw et al., 2005). Despite the unusual features of the sample and the poor generalizability, this unique investigation strongly suggests that childhood bipolar prodromes may be detectable almost a

decade prior to the onset of the full clinical disorder. Importantly, they also suggest that prodromal symptoms may display episodicity during childhood. These findings set the stage for further investigation of such prodromes in general population samples.

Endophenotypes in childhood bipolar disorder

Although endophenotypes do not represent prodromes, they are relevant to investigations of prodromes in that they have utility in the early identification of individuals at risk for specific disorders prior to the onset of clinical symptoms. An endophenotype is a heritable biological trait that may serve as a marker of risk for a later disorder. An endophenotype is distinct from a more general biological marker on the basis of clear genetic or heritability indicators (Gottesman & Gould, 2003). To be useful as clinical predictors, endophenotypes should be specific and sensitive. Gottesman and Gould (2003) outline the following required features to meet criteria for an endophenotype: 1) association with a disorder, 2) primarily state independent, 3) increased prevalence in non-affected family members, and 4) co-segregation of endophenotype and illness within families. While investigations of endophenotypes for childhood bipolar disorder are relatively scant and new, some evidence for deficits in executive function, sustained attention, and emotion labeling have been provided (reviewed below). These findings taken together suggest that the continued search for endophenotypic markers of bipolar disorder would be worthwhile (Glahn, Bearden, Niendam, & Escamilla, 2004).

Facial emotion labeling deficits—Several investigations have now suggested that bipolar children show deficits in the capacity to label emotions from facial expressions (McClure et al., 2005; Rich et al., 2006; Schenkel, Pavuluri, Harral, & Sweeney, 2007). Meeting the state independence feature of an endophenotype, these deficits were also found during euthymic phases of the illness. Based on these findings, Brotman et al. (2008) investigated whether such deficits could also be detected in the unaffected children or siblings of bipolar individuals, another key endophenotype criterion. Deficits in emotion labeling of facial expression were also found in unaffected relatives when compared to healthy control subjects while no differences between this group and the bipolar relatives were found. Based on these findings and the face validity of the principle that the ability to regulate emotion is a primary deficit in bipolar disorder, a focus on emotion processing and regulation in future searches for prodromal markers are warranted.

Neuropsychological markers—Neuropsychological deficits have been reported in bipolar disorder, along with evidence that these deficits may be evident even during euthymic periods (Glahn et al., 2004; Rubinsztein, Michael, Paykel, & Sahakian, 2000). Several studies have reported verbal memory and executive deficits in the unaffected relatives of bipolar individuals (Gilvarry et al., 2001; Keri, Kelemen, Benedek, & Janka, 2001; Zalla et al., 2004). One twin study that assessed neuropsychological functioning in monozygotic twins discordant for bipolar disorder reported deficits in verbal and working memory in healthy co-twins (Gourovitch et al., 1999). Evidence that several other areas of cognitive functioning remain unimpaired has suggested that these skills could be more specific endophenotypes of bipolar disorder (as they meet at least 2 of the required criteria outlined above).

Longitudinal studies also provide support for neuropsychological deficits as possible endophenotypes of bipolar disorder. Unique findings from a very large cohort of males in the Finnish Defense Forces inform this area. Subjects were studied longitudinally to investigate the relationship between general cognitive abilities and other more specific neuropsychological skills and risk for later psychotic disorders. Findings demonstrated that deficits in visual-spatial abilities were associated with later schizophrenia and bipolar

disorder. However, notably, this deficit combined with high arithmetic abilities emerged as a more specific marker of increased risk for later bipolar disorder (Tiihonen et al., 2005). The authors suggest that the capacity for rapid cognitive processing, required for the mathematical skills, may be similar to the neurobiological characteristics of high alertness and psychomotor activity known in manic states. In a smaller and more circumscribed study of the offspring of bipolar parents, an association between performance on the Wisconsin Card Sorting Test (WCST) and later risk for the development of bipolar disorder was reported (Meyer et al., 2006). Despite these suggestive neuropsychiatric findings, their lack of specificity overall limits the clinical and research utility of these findings.

Biological markers pertinent to prodromes

Hypothalamic-pituitary-adrenal (HPA) axis—Increased activity in the HPA axis has been associated with mood disturbances. However, little is known about whether HPA abnormalities predate the onset of mood disorders. The majority of studies exploring the dysregulation of HPA axis functioning have focused on adults, with few studies that have explored this issue in BPD children. Ellenbogen, Hodgins, Walker, Couture and Adam (2006) found that high-risk offspring of parents with BPD had higher afternoon cortisol levels in their natural environment than low-risk offspring. Similar results were found in adolescent offspring of BPD parents (Ellenbogen, Hodgins, & Walker, 2004). While the significance of these findings remains unclear, and alterations in the HPA axis are known in many disorders and thus appear relatively non-specific, they could suggest that altered functioning of the HPA axis may represent one early but non-specific alteration associated with the development of BPD in children.

Neuroimaging studies—Both functional and structural neuroimaging studies have been conducted in the search for brain changes associated with BPD. Frazier et al. (2005) have provided a review of neuroimaging publications within a 15-year span (January 1990 to January 2005) that focused on childhood onset BPD. Frazier et al. (2005) summarized that structural MRI studies have reported numerous differences in BPD children compared to controls, including smaller total cerebral volumes, increased number of white matter hypersensitivities and differences in the size of limbic structures key to emotion processing (smaller amygdala and hippocampus). DeBello, Adler, and Strakowski (2006) have suggested that the finding of smaller amygdala in BP children contrasting with reports of larger amygdala in BP adults could suggest that abnormal amygdala development may be key to the disorder. Dickstein et al. (2005) found that BPD children had reduced gray matter volume in the dorsolateral prefrontal cortex, a structure thought to be involved in the regulation of emotional responses. Gogtay et al. (2007) examined cortical development in children with atypical psychosis before and after the onset of BPD and reported that brain changes were bilaterally asymmetrical with a trajectory characterized by cortical gray matter volume increase on the left and loss on the right after onset of illness. Additionally, there was bilateral loss in the cingulate cortices, a structure also known to be involved in mood regulation. Frazier et al. (2007) examined the brain structure of children with BPD compared to those at risk for BPD and found that BPD children had decreased fractional anisotropy (FA) in the superior longitudinal fasciculus I (SLF I) and the at-risk group showed a similar pattern in the SLF I although at reduced magnitude. Ladouceur et al. (2008) examined healthy offspring of bipolar parents and found an increase in gray matter volume in the parahippocampal/hippocampal areas compared to healthy controls, suggesting a potential neural marker for BPD risk.

In reviewing functional imaging studies, Frazier et al. (2005) concluded that BPD was associated with differences in the activation in the left putamen, thalamus, bilateral anterior cingulate gyrus, left dorsolateral prefrontal cortex, right inferior frontal gyrus, right insula,

and left middle/superior frontal gyrus; all areas known to be involved in affect regulation. Rich et al. (2006) found functional deficiencies in the amygdale–striatal–ventral prefrontal cortex circuit when BPD children attended to a facial emotion or their emotional response to a face, suggesting deficient emotion-attention interactions in BPD youth. In exploring the association of motor inhibition with pediatric BPD, Leibenluft and colleagues (2007) found that children with BPD have difficulties engaging striatal structure and the right ventral prefrontal cortex during unsuccessful inhibition.

Frazier et al. (2005) also reviewed metabolic and biochemical alterations in the brain reported in pediatric BPD. Specifically, the disorder was associated with elevated amino acids in the frontal lobe and basal ganglia, decreased N-acetyl aspartate (a marker of neuronal integrity) in the frontal lobes and increased myo-inositol in the frontal lobe and anterior cingulate gyrus. The authors suggest that biochemical dysregulation in the frontal lobe and basal ganglia may be a marker of childhood BPD. The existing neuroimaging studies on childhood onset BPD and children at risk suggest a potential association with functional, structural, and biochemical alterations evident in structures known to be involved in mood regulation. Despite these promising findings, research does not yet paint a clear and coherent picture of brain changes associated with childhood bipolar disorder that might lead to endophenotypic markers in the brain.

Early temperamental markers for later bipolar disorder

There has been a great deal of interest in the identification of early temperamental markers that may serve as harbingers of risk for later psychopathology (for review see Nigg, 2006). These signs, although potentially useful to target prevention, differ from prodromes as they are not thought to be an early manifestation of symptoms but rather serve as markers of individuals at higher risk to develop specific forms of psychopathology when exposed to certain life experiences or other risk conditions. Whether temperamental traits might also be classified as an endophenotype depends upon whether they meet the criteria as defined above. Temperament is of particular interest in the search for early markers of risk based on the notion that it may represent one of the earliest phenotypic representations of genetic risk. Related to this, it may also represent a feature that makes an individual more vulnerable to psychosocial risk during development.

Behavioral disinhibition—Along this line, several longitudinal studies have investigated the link between early behavioral disinhibition (BD), a stable temperamental feature evident in early childhood and characterized by high novelty seeking and approach, and later risk for psychopathology. BD is also known to be associated with a low threshold for arousal and related high emotional reactivity. Increased risk for later oppositional defiant disorder (ODD), ADHD, and other disruptive behavioral disorders related to early behavioral disinhibition have been reported (Hirshfeld-Becker et al., 2002; Hirshfeld et al., 1992; Rubin, Burgess, Dwyer, & Hastings, 2003). Based on the hypothesis that this temperamental feature may be on a continuum with symptoms of bipolar disorder and therefore could serve as an early marker, Hirshfeld-Becker et al. (2003) investigated whether BD could be such a marker early in life. Utilizing an observational measure of early temperament, and focusing on behavioral disinhibition, Hirshfeld-Becker et al. (2006) studied the high-risk offspring of parents with mood and anxiety disorders and low-risk control groups at 21 months of age. Subsequent follow-up 5 years later at age 6 showed that behaviorally disinhibited toddlers had higher rates of mood and comorbid disruptive behavioral disorders. These observational longitudinal findings suggest that further follow-up into later childhood could reveal more cases of bipolar disorder. Based on these findings the investigators suggest that these early temperamental markers may be targets for preventive interventions.

Parent report measure of temperament—In keeping with the findings from observational longitudinal studies reported above, several investigations of the high-risk offspring of bipolar parents have detected unique temperamental characteristics. Chang, Blasey, Ketter, and Steiner (2003) found increased approach and rhythmicity-sleep scores in the group at high risk for bipolar disorder compared to the general population. An association between high emotionality and unipolar depression was also detected in another high-risk cohort (Duffy, 2007). Further, related to these findings, ‘cyclothymic’ temperament was found to be a predictor of switching to bipolar disorder in a population of children and adolescents with major depressive disorder (MDD) (Kochman et al., 2005).

Emotion regulation—One potentially promising area that might be subsumed under the more general category of temperament is whether early and stable aspects of emotion functioning or emotionality might be useful as markers of BPD. Since BPD is characterized by a fundamental impairment in the ability to manage or regulate emotions as evidenced by mood lability and high intensity of emotional experiences, the early developmental task of emotional regulation may be of interest in explorations of precursor or prodromal states. Emotion regulation, defined as ‘the process of initiating, maintaining, modulating, or changing the intensity, or duration of internal feelings states’, is on a steep developmental trajectory in early childhood (Thompson, 1994). The idea that impaired emotion regulation may be a feature of early onset bipolar disorder has been proposed (Luby, Belden, & Tandon, in press). Further, preliminary empirical evidence demonstrating that young children who meet criteria for BPD display emotions (in response to incentive events) with greater intensity and for longer durations than healthy controls has also been provided (Luby, Tandon, & Belden, 2009b).

Early developmental studies, with small sample sizes but utilizing observational measures, reported alterations in several dimensions of emotion development in the preschool offspring of bipolar parents (Zahn-Waxler, Cummings, McKnew, & Radke-Yarrow, 1984; Zahn-Waxler, McKnew, Cummings, Davenport, & Radke-Yarrow, 1984). Consistent with these early observations, Chang, Steiner, and Ketter (2000) using larger high-risk samples and different methods reported increases in ‘mood regulation problems’ evidenced by higher levels of rejection sensitivity and problems with ‘resolution of emotional response’ in the high-risk offspring of parents with bipolar disorder. Impairment in emotion regulation as a possible early sign of risk for bipolar disorder has also been proposed by Hirshfeld-Becker et al. (2003). Along this line, several studies of the high-risk offspring of mood disordered parents have detected alterations in measures of emotionality (Clark, Watson, & Mineka, 1994; Kelvin, Goodyer, & Altham, 1996). However, one important way in which this model fails to map onto the deficits known in bipolar disorder is that emotion regulation is a stable trait, while the dysregulation known in bipolar disorder is frequently episodic. Further investigations of the temporal features of emotion regulation as a marker of risk for later childhood bipolar disorder, and whether episodicity is a key feature or not (an issue of significant controversy in the nosology of BPD), would be of interest.

Other forms of psychopathology as markers of risk for later bipolar disorder

Several studies have investigated the question of whether early onset forms of non-bipolar psychopathology may be markers of later childhood bipolar disorder. Such findings would suggest that there is heterotypic continuity between early childhood disorders and later childhood bipolar disorder. Perhaps the most well-studied area in this domain is the question of whether children with MDD later switch to bipolar disorder. Numerous studies have reported rates of switching ranging from 20 to 49% among depressed children and adolescents (Geller, Fox, & Clark, 1994; Geller, Zimmerman, Williams, Bolhofner, & Craney, 2001; Strober, Lampert, Schmidt, & Morrell, 1993). In keeping with these rates of

switching, Duffy et al. (Duffy, Alda, Crawford, Milin, & Grof, 2007) reported that 33% of subjects with a diagnosis of MDD later met criteria for bipolar disorder. Other notable findings from this study were that nonspecific precursors of later bipolar disorder, in particular mood and anxiety disorders, were also found. Longitudinal studies have demonstrated that depressive symptoms were manifest prior to the emergence of hypomanic or manic episodes in bipolar samples (Egeland et al., 2003; Shaw et al., 2005; Hillegers et al., 2005). The rates of switching found suggest that clinicians should be vigilant about the development of mania in children with depression when other risk factors (e.g., family history) are also present.

Exploratory of mania manifestations in very early childhood: possible relevance to prodromes

Potentially related to the question of whether prodromes for childhood bipolar disorder can be identified, there has been increasing interest in and empirical support for the identification of depressive disorders, and some emerging evidence suggesting that mania symptoms or syndromes may also arise earlier in life during the preschool period of development (Luby & Belden, 2006; Luby, Si, Belden, Tandon, & Spitznagel, 2009a; Luby et al., 2009b; Stalets & Luby, 2006). Numerous case reports and retrospective chart reviews have described mania manifestations in very young children (Luby, Tandon, & Nicol, 2007; Scheffer & Niskala Apps, 2004; Tumuluru, Weller, Fristad, & Weller, 2003; Wilens et al., 2003). Early identification of several very early onset mental disorders has facilitated early intervention and prevention, a strategy that has led to surprisingly good outcomes in several areas of psychopathology (Choate, Pincus, Eyberg, & Barlow, 2005; Rebecca, 2007; Scheeringa et al., 2007). Along this line, the identification of age-adjusted mania symptoms at very early developmental periods, and potentially prior to the full-blown manifestation of bipolar disorder, could inform the search for early prodromes and be important for the application of preventive interventions. Currently, investigations of mania symptoms in children under the age of 6 remain highly exploratory. However, given the progress in the assessment and identification of mood symptoms and disorders in very young children (Egger, Ascher, & Angold, 1999; Luby, Heffelfinger, Koenig-McNaught, Brown, & Spitznagel, 2004) this is an area for future exploration.

Preventive interventions for childhood bipolar disorder

In addition to the difficulty of accurate diagnosis of BPD in childhood, effective treatments have proven even more elusive. Based on this, the application of preventive interventions during prodromal periods is made even more important. While this is a largely under-explored area, several investigations of pharmacotherapies have been conducted in childhood populations at high risk to develop BPI on the basis of presence of other Axis I disorders and/or milder variants of BPD (Chang et al., 2003; DelBello, Adler, Whitsel, Stanford, & Strakowski, 2007; Findling et al., 2005). All of these studies showed promising results; however, two of the three (Chang and Del-Bello) were open trials. While these three investigations were conducted in populations with related Axis I disorders and high-risk status by virtue of other related BP characteristics, significant caution is advised in the use of pharmacologic agents in high-risk children based on increasing data demonstrating metabolic and other side effects of mood stabilizing agents (Correll et al., 2009). Alternatively, and of increasing potential importance based on greater clarity about side effects of mood stabilizers, is the increasing body of empirical evidence supporting the efficacy of psychotherapeutic strategies, in particular Family Focused Therapy (FFT) both as an adjunct to medication in affected children and more recently as a prevention strategy (Miklowitz, Biuckians, & Richards, 2006, 2007). The use of an adapted version of this treatment as a preventive intervention has also been developed and has shown promise in preliminary studies (Miklowitz & Chang, 2008).

Conclusion

There has been very limited investigation of early prodromes for later childhood bipolar disorder. This is remarkable in light of intriguing evidence from several studies reviewed above suggesting that an identifiable prodrome may arise many months and even many years prior to the onset of the full clinical disorder in childhood. The need for further research focus in this area is underscored by the known severity, chronicity, and the relapsing and treatment-resistant course of this disorder. Based on the promising findings of prodromes as well as high-risk states and possible endophenotypic markers reviewed above, further more controlled and targeted investigations into the early markers of bipolar disorder appears warranted and potentially fruitful. Future studies should move into larger epidemiological samples and will require blind longitudinal designs to build on the limited existing data. Given that individuals at higher risk for the disorder can be identified based on family history of the disorder in relatives, high-risk subgroups within a larger epidemiological sample would be highly feasible to ascertain and are necessary to capture a sufficient number of cases. Further, the high rates of comorbid disorders known in childhood bipolar disorder suggest that it would be very important to carefully assess and control for comorbidity to more accurately inform the characteristics of bipolar prodromes in these longitudinal study designs. Such large-scale longitudinal studies are justified by the possibility that the identification of a prodrome could be useful not only to target individuals for intervention prior to the first onset of mania, but also to better predict and perhaps forestall recurrent mania episodes. Until such longitudinal studies with appropriate controls are conducted, specific and clinically useful markers for bipolar prodromes will remain elusive.

Key points

- Childhood bipolar disorder remains a difficult disorder to treat effectively.
- Several studies suggest prodromal states can be identified prior to the onset of the clinical disorder in high-risk samples.
- Endophenotypes and other biological markers for childhood bipolar disorder have also been identified.
- Further large-scale studies are now needed to aid in the sensitive and specific identification of prodromes for childhood bipolar disorder.
- Some promising preventive interventions have been identified, underscoring the importance of identifying prodromal states in this difficult to treat disorder.

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Table 1

Characteristics of empirical studies relevant to prodromes

Author	Design	Sample size	Interviewees	Treatment effects considered	Environmental stressors considered	Comorbidity addressed
Direct investigations of mania prodromes in childhood: prospective and retrospective studies						
Lish et al., 1994	Cross-sectional (non-blind/no control)	500 bipolar DMDA members	Child (retrospective)	No	No	No
Correll et al., 2007	Retrospective (non-blind/no control)	34 mania w/psychosis 18 mania w/o psychosis	Child and/or parent	No	No	Yes
Shaw et al., 2005	Longitudinal prospective (blind/control)	110 at-risk children with BPI parent 112 children with well parents	Parent	No	No	No
Egeland et al., 2003	Longitudinal prospective (non-blind/control)	100 Children with BPI parent 110 Matched control sample	Parent	No	No	No
Egeland et al., 2000	Retrospective (blind/no control)	58 BPI cases	Parent	No	No	No
Endophenotypes for childhood bipolar disorder						
Schenkel et al., 2007	Cross-sectional (blind/control)	29 unmedicated/acute ill 29 medicated/clinically stabilized	Child, parent	Yes	No	Yes
Brotman et al., 2008	Cross-sectional (non-blind/control)	52 youth w/BPD 24 at risk youth 78 control	Child	No	No	Yes
Rich et al., 2006	Cross-sectional (non-blind/control)	22 BP children 21 controls	Child	Yes	No	Yes
McClure et al., 2005	Cross-sectional (non-blind/control)	40 youths with BP 22 comparison subjects	Child, parent	No	No	Yes
Early temperamental markers for later bipolar disorder						
Kochman et al., 2005	Longitudinal (non-blind/no control)	80 children/adolescents inpatient admissions who met MDD criteria	Child, parent	Yes	No	Yes
Chang et al., 2000	Cross-sectional (blind/no control)	60 offspring of bipolar adults	Child, parent	No	Yes	Yes
Duffy et al., 2007	Longitudinal (blind/control)	75 Offspring of bipolar and well parents (50, high-risk affected, 25, high-risk unaffected)	Child, parent	No	Yes	No
Chang et al., 2003	Cross-sectional (blind/no control)	53 offspring of at least one bipolar parent	Child, parent	No	No	Yes
Hirshfeld-Becker et al., 2006	Cross-sectional (blind/control)	278 offspring of parents w/panic disorder or MDD 34 offspring of BP parents	Child (if age 12 or older), parent	No	No	Yes
Kelvin et al., 1996	Cross-sectional (non-blind/control)	21 youth w/MDD 8 youth w/ Anxiety	Child, sibling	No	No	Yes
Zahn-Waxler, Cummings et al., 1984	Longitudinal (blind/control)	7 males with a BPD parent	Parent and observations of child	No	No	No

Author	Design	Sample size	Interviewees	Treatment effects considered	Environmental Stressors considered	Comorbidity addressed
Zahn-Waxler, McKnew et al., 1984	Longitudinal (blind/control)	7 males with a BPD parent	Parent, observations of child	No	No	No
Other forms of psychopathology as markers of risk for later bipolar disorder						
Geller, Fox, and Clark, 1994	Prospective (blind/control)	79 6 to 12 yr olds with MDD	Child, parent	Yes	Yes	Yes
Geller et al., 2001	Prospective (blind/control)	72 adults with MDD diagnoses in childhood	Child (retrospective)	Partially *	No	Partially *
Duffy et al., 2007	Longitudinal (blind/control)	67 offspring of LiResponders 60 offspring of Li non-responders 61 control	Child, parent	No	No	Yes
Strober et al., 1993	Longitudinal prospective (non-blind/no control)	58 adolescents with MDD	Child	No	No	No

* Children with ADHD were excluded at study onset because the response of comorbid ADHD to medication treatment might confound ratings of major depressive disorder.