Editorial

Bipolar disorder in children and adolescents – are we approaching the final frontier?

Recent studies suggest that the onset of bipolar disorder most commonly occurs before age 18 (1–2). However, the clinical presentation of bipolar disorder in youth often differs from that in adults. Children and adolescents with bipolar disorder have higher rates of mixed episodes, rapid cycling, and co-occurring attention-deficit/hyperactivity disorder (ADHD) as compared to adults with bipolar disorder. It remains to be determined whether these age-related differences are the result of developmental differences in expression of the same symptoms or distinct underlying genetic and neurophysiological abnormalities marking pediatric- and adult-onset bipolar disorder as two different disorders. The results of recent neuroimaging and pharmacological intervention investigations reveal that children and adolescents with bipolar disorder exhibit distinct patterns of pharmacological response and neurobiological alterations compared to adults with bipolar disorder (3–6). However, these differences might be due to reasons other than distinct neuropathophysiology between the two conditions. As discussed below, adults with bipolar disorder often have had many years of illness during which the sequela of this devastating disorder may have exerted effects on the brain.

While researchers continue to explore potential neurobiological and genetic etiologies of bipolar disorder through studies of adult probands, there are several advantages to including pediatric populations in these studies. First, family studies suggest that youth with bipolar disorder may have a greater genetic load for this illness than adults with bipolar disorder (7). Therefore, relatively small effects from single genetic polymorphisms may be amplified in samples of patients with pediatric bipolar disorder. Subsequently, this enhanced genetic susceptibility may be reflected in enhanced neurobiological abnormalities that may be more readily detected in sample sizes typically used for neuroimaging studies (12–40 subjects). Children and adolescents with bipolar disorder also are typically closer to their illness onset than adults, providing a window of opportunity for identifying genetic and neurobiological trait characteristics of the illness (i.e., disease biomarkers) that are independent of repeated affective episodes and other confounding factors associated with illness course, such as co-occurring substance use and medical disorders, as well as medication exposure. Longitudinal follow up from childhood to adulthood could then shed light on the developmental course of the disorder, linking findings from adult studies to those from pediatric studies. Finally, clarifying the genetic and neurophysiological characteristics of pediatric bipolar disorder may lead to identifying biomarkers that could serve as predictors of treatment response, targets for developing novel treatments, and signals for impending development of bipolar disorder. These signals could then be useful for identifying individuals who might benefit from early intervention to halt or delay the development of fully expressed bipolar disorder.

During the past decade evidence-based research has shifted the debate from whether bipolar disorder in children and adolescents exists to how to best use biological research to determine core trait characteristics of bipolar disorder that might be used as predictors of illness development. In this special issue of *Bipolar Disorders* we begin with a broad overview examining the current controversies regarding the phenomenology of bipolar disorders in youth and then move beyond the confusion and take a journey into the next generation of research that will utilize innovative techniques to further advance our understanding of the genetic and neurobiological basis of this illness as it presents in children and adolescents.

The first article is an eloquent meta-analysis of the phenomenological characteristics of mania in children and adolescents by Kowatch *et al.* (8). The enlightening findings of this paper suggest that, after statistically accounting for methodological differences among phenomenological studies, there is more consistency in the description of pediatric bipolar disorder over the last 25 years than disagreement. This conclusion is reassuring as we, as a field, need to establish diagnostic consistency in order to be able to confidently explore the biology of bipolar disorder. Soutullo *et al.* (9) provide an
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International prospective on pediatric bipolar disorder by reviewing studies of clinical samples from outside the United States (US). In this review the authors provide several explanations for the disparity in rates of pediatric bipolar disorder between the US and other countries, including diagnostic and study design biases as well as the potential that higher use of stimulants and antidepressants in children in the US may be triggering bipolar disorder earlier, leading to higher rates of pediatric bipolar disorder than is found in other countries.

Two papers in this special issue describe the utility of commonly used self-report and parent-report measures to accurately diagnose children and adolescents with bipolar disorder in academic and clinical settings, where there may exist both underdiagnosis and overdiagnosis. Youngstrom et al. (10) assess the diagnostic efficiency of the Parent and Adolescent Self-report versions of the Mood Disorder Questionnaire, the General Behavior Inventory, and the Young Mania Rating Scale in an academic and community setting, and Faraone et al. (11) evaluate the sensitivity and specificity of a novel Child Behavior Checklist Juvenile Bipolar Disorder subscale score. These ratings may be useful as screening instruments for pediatric bipolar disorder in clinical settings and to define more homogeneous groups of subjects for biological research studies.

Rates of attempting and completing suicide in bipolar disorder are elevated compared with the general population and suicide risk is greatest in childhood compared with adult-onset bipolar disorder (12). Therefore, identifying risk factors associated with suicide attempts and whether these risk factors are distinct from those associated with adult bipolar disorder is an important area of investigation that Goldstein et al. (13) present in their study, which is the first to examine rates of and risk factors for suicide attempts in pediatric bipolar disorder.

The next group of articles focuses on examples of how neuropsychological tests and neuroimaging studies may be used to characterize neurophysiological abnormalities and endophenotypes of bipolar disorder in children and adolescents. Although difficult to measure in a controlled laboratory setting, abnormalities in response to reward and punishment are clinical characteristics observed in children and adolescents with bipolar disorder. Rich et al. (14) describe their work using an affect-modulating startle task to examine potential differences in reactivity to emotional stimuli (reward and punishment) among children and adolescents with bipolar disorder and healthy controls. Work-
a putative marker of neuronal integrity, was present in bipolar children and adolescents with a family history of bipolar disorder (20). In a follow-up to this study, Gallelli et al. (21) investigate whether this previously identified abnormality is a trait marker by evaluating whether it is also present in youth at risk for developing bipolar disorder.

The next two papers focus on the genetics of pediatric bipolar disorder. In the first, Althoff et al. (22) review and compare findings from family, twin, adoption, and molecular genetic studies of adult and pediatric bipolar disorder and offer suggestions for future directions of research. The second paper is an example of a novel approach to using genetics for identifying endophenotypes of bipolar disorder in children and adolescents. Geller et al. (23) present findings from a study that examines the relationship between the arginine vasopressin V1a receptor promoter region microsatellite repeat and hypersexuality and uninhibited people-seeking behaviors in bipolar youth.

Finally, the last two papers of this special issue focus on children at relatively high risk for developing bipolar disorder, based on a parental history of bipolar disorder. Romero et al. (24) remind us that in addition to neurobiological and genetic contributions, family environmental influences may also impact the onset and prognosis of youth with and at familial risk for developing bipolar disorder. Findling et al. (25) present their study which begins to characterize what may be a prodromal presentation of bipolar disorder in youth at familial risk for developing bipolar disorder; ‘cycloaxia’. Identifying prodromal manifestations of pediatric bipolar disorder is an essential initial step to understanding the development of bipolar disorder and establishing targeted early intervention strategies.

The collection of papers that we present in this special issue of Bipolar Disorders clearly demonstrates that the field of pediatric bipolar disorder has made exciting research advances over the past decade. Although we have seen enormous progress in our understanding of this disorder, many pressing questions remain. Do children and adolescents with bipolar disorder grow up to become adults with bipolar disorder? Are there specific lifelong psychological, neurobiological, or genetic effects of having the onset of bipolar disorder during a developmentally sensitive period? Why is the clinical manifestation of pediatric bipolar disorder distinct from that of adult bipolar disorder? Are there useful biological markers that will distinguish pediatric bipolar disorder from other childhood psychiatric disorders and thus aid in diagnosis? Lastly and most importantly, how can we apply the knowledge gained from biological studies to achieve the ultimate goal of early recognition and intervention, so that we may begin to decrease the morbidity and mortality associated with lifelong bipolar disorder.

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References


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