Bipolar Disorders 2005: 7: 479–482

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 sequlae 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

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. Working from findings of verbal memory deficits in adults with bipolar disorder, **Glahn et al. (15)** next present their study identifying verbal memory abnormalities in children and adolescents with bipolar disorder. Studies of abnormalities in neuropsychological domains are useful to determine targets for intervention strategies, such as making educational accommodations, and to design tasks that may be used in functional neuroimaging studies in order to examine regional abnormalities in brain activation. Consistent with the finding of verbal memory deficits, **Frazier et al. (16)** examined cortical gray matter volume abnormalities in children and adolescents with bipolar disorder and found abnormalities in parietal and temporal gray matter regions that are involved in verbal memory, attention control, and facial recognition.

Decreased amygdala volume is one of the most consistent findings that has emerged from structural neuroimaging studies of bipolar youth. Although this finding is not necessarily specific to pediatric bipolar disorder, as it also has been described in pediatric depression (17), it is in contrast to studies of adults with bipolar disorder that have reported enlarged or normal amygdala volumes. Longitudinal neuroimaging studies could help explain these discrepant findings. In the first published longitudinal imaging study of children and adolescents with bipolar disorder, **Blumberg et al. (18)** determine that decreased amygdala volume persists over a 2-year period. This finding suggests that smaller amygdalae may be a stable marker for early-onset bipolar disorder, but the reasons for different findings in adults remain unclear.

Functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS) are two other neuroimaging techniques that allow for the assessment of brain function and neurochemistry. **Adler et al. (19)** used fMRI to distinguish between adolescents with bipolar disorder with and without comorbid ADHD. ADHD commonly co-occurs with bipolar disorder in children and adolescents; however, the relationship between these illnesses remains unclear. An understanding of how brain activation patterns differ in bipolar children with and without ADHD may clarify the relationship between ADHD and bipolar disorder as well as add to our knowledge of the neurophysiological link between attention and mood. MRS is a powerful neuroimaging tool that may be useful for identifying neurochemical abnormalities and neurochemical effects of medications and predictors of treatment response in bipolar youth. In a prior study Chang et al. identified that reduced dorsolateral prefrontal cortical *N*-acetylaspartate,

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; 'cyclotaxia'. 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.

We would like to thank all contributors to this issue for their diligent efforts to provide us with the latest update of their research endeavors. We would also like to thank the Editors of *Bipolar Disorders*, Dr Samuel Gershon and Dr Roy Chengappa, as well as Ms Donna Kocan, the Managing Editor, for their interest and willingness to devote an entire issue of *Bipolar Disorders* to the topic of pediatric bipolar disorder and for their invaluable support throughout the process of assembling this special issue.

Melissa P DelBello
Kiki D Chang

References

1. Perlis RH, Miyahara S, Marangell LB et al. STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2004; 55: 875–881.
2. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. J Affect Disord 1994; 31: 281–294.
3. Adleman NE, Barnea-Goraly N, Chang KD. Review of magnetic resonance imaging and spectroscopy studies in children with bipolar disorder. Expert Rev Neurother 2004; 4: 69–77.
4. Kowatch RA, DelBello MP. Pharmacotherapy of children and adolescents with bipolar disorder. Psychiatr Clin North Am 2005; 28: 385–397.
5. DelBello MP, Findling RL, Kushner S et al. A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005; 44: 539–547.
6. Frazier JA, Ahn MS, DeJong S, Bent EK, Breeze JL, Giuliano AJ. Magnetic resonance imaging studies in early-onset bipolar disorder: a critical review. Harv Rev Psychiatry 2005; 13: 125–140.
7. Todd RD. Genetics of early onset bipolar affective disorder: are we making progress? Curr Psychiatry Rep 2002; 4: 141–145.
8. Kowatch RA, Youngstrom EA, Danielyan A, Findling RL. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. Bipolar Disord 2005; 7: 483–496.
9. Soutullo CA, Chang KD, Díez-Suárez A et al. Bipolar disorder in children and adolescents: international perspective on epidemiology and phenomenology. Bipolar Disord 2005; 7: 497–506.
10. Youngstrom E, Meyers O, Demeter C et al. Comparing diagnostic checklists for pediatric bipolar disorder in academic and community mental health settings. Bipolar Disord 2005; 7: 507–517.

11. Faraone SV, Althoff RR, Hudziak JJ, Monuteaux M, Biederman J. The CBCL predicts DSM bipolar disorder in children: a receiver operating characteristic curve analysis. Bipolar Disord 2005; 7: 518–524.
12. Brent DA, Perper JA, Goldstein CE et al. Risk factors for adolescent suicide. A comparison of adolescent suicide victims with suicidal inpatients. Arch Gen Psychiatry 1988; 45: 581–588.
13. Goldstein TR, Birmaher B, Axelson D et al. History of suicide attempts in pediatric bipolar disorder – factors associated with increased risk. Bipolar Disord 2005; 7: 525–535.
14. Rich BA, Bhangoo RK, Vinton DT et al. Using affect-modulated startle to study phenotypes of pediatric bipolar disorder. Bipolar Disord 2005; 7: 536–545.
15. Glahn DC, Bearden CE, Caetano S et al. Declarative memory impairment in pediatric bipolar disorder. Bipolar Disord 2005; 7: 546–554.
16. Frazier JA, Breeze JL, Makris N et al. Cortical gray matter differences identified by structural magnetic resonance imaging in pediatric bipolar disorder. Bipolar Disord 2005; 7: 555–569.
17. Rosso IM, Cintron CM, Steingard RJ, Renshaw PF, Young AD, Yurgelun-Todd DA. Amygdala and hippocampus volumes in pediatric major depression. Biol Psychiatry 2005; 57: 21–26.
18. Blumberg HP, Fredericks C, Wang F et al. Preliminary evidence for persistent abnormalities in amygdala volumes in adolescents and young adults with bipolar disorder. Bipolar Disord 2005; 7: 570–576.
19. Adler CM, DelBello MP, Mills NP, Schmithorst V, Holland S, Strakowski SM. Comorbid ADHD is associated with altered patterns of neuronal activation in adolescents with bipolar disorder performing a simple attention task. Bipolar Disord 2005; 7: 577–588.
20. Chang K, Adleman N, Dienes K, Barnea-Goraly N, Reiss A, Ketter T. Decreased *N*-acetylaspartate in children with familial bipolar disorder. Biol Psychiatry 2003; 53: 1059–1065.
21. Gallelli KA, Wagner CM, Karchemskiy A et al. *N*-acetylaspartate levels in bipolar offspring with and at high-risk for bipolar disorder. Bipolar Disord 2005; 7: 589–597.
22. Althoff RR, Faraone SV, Rettew DC, Morley CP, Hudziak JJ. Family, twin, adoption, and molecular genetic studies of bipolar disorder. Bipolar Disord 2005; 7: 598–609.
23. Geller B, Tillman R, Badner JA, Cook EH Jr. Are the arginine vasopressin V1a receptor microsatellites related to hypersexuality in children with a prepubertal and early adolescent bipolar disorder phenotype? Bipolar Disord 2005; 7: 610–616.
24. Romero S, DelBello MP, Soutullo CA, Stanford K, Strakowski SM. Family environment in families with versus families without parental bipolar disorders – a preliminary comparison study. Bipolar Disord 2005; 7: 617–622.
25. Findling RL, Youngstrom EA, McNamara NK et al. Early symptoms of mania and the role of parental risk. Bipolar Disord 2005; 7: 623–634.

Corresponding author:
Melissa P DelBello, MD
Division of Bipolar Disorders Research
Department of Psychiatry
University of Cincinnati College of Medicine
231 Bethesda Avenue, ML 559
Cincinnati, OH 45267, USA.
Fax: (513) 558 3399;
e-mail: delbelmp@email.uc.edu