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Pediatric Bipolar Disorder Comes of Age

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Extending previous seminal work on pediatric bipolar disorder (BD), Geller et al¹ present the first longitudinal study following up a large sample of youth diagnosed with pediatric BD into adulthood. Beginning when the subjects had a mean (SD) age of 11.1 (2.6) years, the investigators followed up 115 patients with BD for 8 years, at which time 54 patients were older than 18 years. Of these, 44% had a manic episode after age 18 years, as ascertained by the Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS), suggesting continuity with previously observed symptoms. Morbidity, in terms of weeks spent ill, was extremely high, and 35.2% had substance abuse disorders. Attrition in the study was remarkably low.

Just as the children in this important study have matured over the last decade, so has research on pediatric BD. PubMed listings indicate that, from 1986 to 1996, 15 articles were published on pediatric BD; in the subsequent decade (1997–2007), that number grew to 294. Indeed, more articles were published on pediatric BD in January 2008 than in the entire decade from 1986 to 1996. This upsurge both results from and contributes to a growing awareness that serious mental illnesses do not emerge de novo when individuals reach adulthood, but rather reflect early developmental processes. This awareness has profound implications for future research, highlighting the need for longitudinal studies such as that of Geller et al¹ as well as pathophysiological research in children, studies comparing adults and youth with BD, and studies of youth at familial risk for BD.

Regarding pediatric BD, what have we learned since 1986? As one might expect in an emerging area of clinical research, most work has focused on phenomenology. First, it is now clear that, using interview techniques closely parallel to those used in adults, children can be identified who clearly meet *DSM-IV* criteria for BD.^{2,3} Thus, consensus has emerged that unequivocal cases of BD occur in prepubertal children as well as in adolescents. However, while there is agreement that classic cases occur, questions remain regarding the boundary of the phenotype; these questions clearly affect the reported prevalence.^{4,5} For example, it has been suggested that a syndrome comprising severe irritability and attention-deficit hyperactivity disorder–like symptoms, without distinct manic episodes, is a developmental presentation of BD. However, such youth have been shown to differ from those with unequivocal *DSM-IV* BD in clinical course, family history, and some, but not all, pathophysiological measures.^{6–9}

Second, we have learned that children with BD, like adults with BD, typically meet criteria for a number of other *DSM* diagnoses.^{1,10–12} It remains to be seen whether this finding reflects true comorbidity, referral bias, limitations in our current diagnostic system, or shared pathophysiology. Third, children diagnosed with BD are typically severely impaired, with frequent relapses and minimal time in remission,^{1–3,12,13} highlighting the great need for rigorous studies of treatment interventions. There is a particular need for randomized, placebo-controlled trials, because preliminary data from such trials suggest that medications frequently

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used to treat pediatric BD show an inconsistent pattern of benefit when compared with placebo.^{14,15} As is the case in pediatric depression, one cannot assume that drugs that are effective in treating adult BD are similarly effective in treating pediatric BD. Furthermore, these medications bear the risk of serious adverse effects, the long-term consequences of which remain poorly understood in children. Cognitive, behavioral, and educational interventions, including those that show promise in adult BD, should also be subject to randomized, controlled trials in pediatric BD.

What will the next decade(s) of research on pediatric BD bring? Without question, future research will stand on the shoulders of the phenomenological studies already mentioned. However, to answer definitively pressing questions about treatment, outcome, and risk, we will need to go beyond phenomenology. Research throughout medicine indicates that advances occur when data on clinical presentation and longitudinal outcome are integrated with data on organ system dysfunction. In psychiatry, this will require research differentiating clinical groups not simply based on symptoms and longitudinal course, but also on pathophysiologic grounds. Thus, we look forward to a time when clinical assessments are augmented by biomarker data.¹⁶⁻¹⁸ Ultimately, this approach may allow us to differentiate pediatric BD from other childhood syndromes characterized by mood symptoms and disruptive behavior, facilitating the development of treatments that are more specific than those currently available.

The conceptual framework underpinning this new era of research in psychiatry emerges from neuroscience, particularly as applied through neuroimaging, and from insights regarding the genetics of complex diseases. From the developmental perspective, it is fortunate that this new conceptual framework can be particularly powerful when applied to pediatric populations. In genetics, findings in diverse areas of medicine suggest that early-onset illness is associated with heavy genetic loading, so studies in pediatric BD may be particularly informative. Indeed, studies report genetic associations in youth with BD;^{19,20} one, from the same sample reported here, found an association with the brain-derived neurotrophic factor gene (*BDNF*), which has also been implicated in BD in adults.²⁰ Given the role of neurotrophins in brain development, research on *BDNF* may be particularly informative in shaping our understanding of BD as a developmental illness. In addition, research on gene $\times$ environment interactions can focus profitably on youth at risk because the environmental component of gene $\times$ environment interactions is likely to involve childhood experiences.²¹

From the neuroimaging perspective, studies in pediatric BD, relative to adult BD, may be less confounded by the effect of longstanding treatment and repeated mood episodes. Also, the fact that early-onset illness tends to be familial and relatively severe may increase the signal to noise ratio in neuroimaging and other pathophysiological studies. Indeed, a recent metaanalysis found that, in youth, but not in adults, with BD, investigators consistently observe decreased amygdala volume in patients compared with controls,²² and a new study suggests that hippocampal abnormalities may be more prominent in youth than in adults with BD.²³ However, to my knowledge, there are no neuroimaging studies comparing adults and youth with BD directly; even neuroimaging studies comparing children and adolescents with BD are lacking. Such research is needed to advance toward the goal of understanding BD as a developmental illness.

Ultimately, however, research on children at risk for BD may generate particularly important insights regarding developmental aspects of BD, because it allows us to study the pathophysiology and symptoms of the illness as it unfolds—or does not unfold. Importantly, most children of parents with BD, despite their relatively high risk for BD, will not develop the illness.²⁴ Nonetheless, BD is clearly very heritable, and research in individuals at risk for schizophrenia, although conducted largely in unaffected adult relatives of probands, provides something of a model for BD. The work in schizophrenia began with careful studies of

neurophysiology and cognitive function in probands and relatives, followed by genetic and imaging studies and their integration, and the development of animal models.²⁵

The literature on endophenotypes in BD lags behind that on schizophrenia, but there are studies of adult relatives of bipolar probands as well as a nascent literature on children at risk.²⁶ The latter suggests that such children may have deficits in cognition²⁷ and the processing of emotional stimuli^{28,29} as well as abnormalities in brain morphometry.^{30,31} Research in children at risk for BD should proceed systematically, beginning with careful observations of, not just symptoms, but affective and cognitive processing in probands, followed by parallel studies in those at risk. Children at risk for BD represent an important public health priority and a relatively unique opportunity to both observe the development of a highly heritable psychiatric illness and to identify factors promoting resilience. Ultimately, the goal would be to design and test interventions aimed at preventing the onset of BD.

Despite the promise of this approach, work in this area will require a concerted effort; research in children presents challenges not present in research with adults. These include subjects' increased vulnerability, the specialized clinical skill required to assess children at different developmental levels, appreciating the pivotal role of parents, potential negative consequences of labeling, and the fact that some important techniques, such as positron emission tomography, are relatively contraindicated. In developing novel therapeutics, children's increased vulnerability leads to justifiable caution, so that novel agents are often used only after they are found to be safe and, to at least some degree, effective in adults.

Finally, investigators studying children study a moving target in that the risk of illness evolves in the context of an individual who is developing rapidly in all domains. Bipolar disorder, with its cycles between depression, mania, and euthymia, is itself something of a moving target, so in research on pediatric BD, complexity abounds. From that perspective, the study by Geller et al¹ is a particularly notable achievement, because such careful longitudinal studies provide an important foundation for future research. The publication of Geller et al¹ in the *Archives* reflects our field's continuing efforts to nurture developmental conceptualizations of psychiatric illnesses. Such conceptualizations hold the hope of fostering work that will allow us to treat youth with BD more effectively and eventually give us the knowledge base needed to prevent the onset of BD in youth at risk. In this way, research in pediatric bipolar disorder will advance as both the field and our patients come of age.

References

1. Geller B, Tillman R, Bolhofner K, Zimmerman B. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. *Arch Gen Psychiatry* 2008;65(10):1125–1133. [PubMed: 18838629]
2. Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Keller M. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry* 2006;63(2):175–183. [PubMed: 16461861]
3. Findling RL, Gracious BL, McNamara NK, Youngstrom EA, Demeter CA, Branicky LA, Calabrese JR. Rapid, continuous cycling and psychiatric comorbidity in pediatric bipolar I disorder. *Bipolar Disord* 2001;3(4):202–210. [PubMed: 11552959]
4. Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry* 2007;64(9):1032–1039. [PubMed: 17768268]
5. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996–2004. *Biol Psychiatry* 2007;62(2):107–114. [PubMed: 17306773]
6. Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, Egger HL, Angold A, Pine DS, Leibenluft E. Prevalence, clinical correlates, and longitudinal course of severe mood and behavioral dysregulation in children. *Biol Psychiatry* 2006;60(9):991–997. [PubMed: 17056393]

7. Brotman MA, Kassem K, Reising MM, Guyer AE, Dickstein DP, Rich BA, Towbin KE, Pine DS, McMahon FJ, Leibenluft E. Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation. *Am J Psychiatry* 2007;164(8):1238–1241. [PubMed: 17671287]
8. Rich BA, Schmajuk M, Perez-Edgar KE, Fox NA, Pine DS, Leibenluft E. Frustration elicits different psychophysiological and behavioral responses in pediatric bipolar disorder and severe mood dysregulation. *Am J Psychiatry* 2007;164(2):309–317. [PubMed: 17267795]
9. Guyer AE, McClure EB, Adler AD, Brotman MA, Rich BA, Kimes AS, Pine DS, Ernst M, Leibenluft E. Specificity of face emotion labeling deficits in childhood psychopathology. *J Child Psychol Psychiatry* 2007;48(9):863–871. [PubMed: 17714371]
10. Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Bridge J, Keller M. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry* 2006;63(10):1139–1148. [PubMed: 17015816]
11. Carlson GA. Mania and ADHD: comorbidity or confusion. *J Affect Disord* 1998;51(2):177–187. [PubMed: 10743850]
12. Biederman J, Faraone SV, Wozniak J, Mick E, Kwon A, Cayton GA, Clark SV. Clinical correlates of bipolar disorder in a large, referred sample of children and adolescents. *J Psychiatr Res* 2005;39(6):611–622. [PubMed: 16009376]
13. DelBello MP, Hanseman D, Adler CM, Fleck DE, Strakowski SM. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. *Am J Psychiatry* 2007;164(4):582–590. [PubMed: 17403971]
14. Wagner KD, Kowatch RA, Emslie GJ, Findling RL, Wilens TE, McCague K, D'Souza J, Wamil A, Lehman RB, Berv D, Linden D. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. *Am J Psychiatry* 2006;163(7):1179–1186. [PubMed: 16816222]
15. Kafantaris V, Coletti DJ, Dicker R, Padula G, Pleak RR, Alvir JM. Lithium treatment of acute mania in adolescents: a placebo-controlled discontinuation study. *J Am Acad Child Adolesc Psychiatry* 2004;43(8):984–993. [PubMed: 15266193]
16. McIntosh AM, Whalley HC, McKirdy J, Hall J, Sussmann JE, Shankar P, Johnstone EC, Lawrie SM. Prefrontal function and activation in bipolar disorder and schizophrenia. *Am J Psychiatry* 2008;165(3):378–384. [PubMed: 18198268]
17. Marsh AA, Finger EC, Mitchell DG, Reid ME, Sims C, Kosson DS, Towbin KE, Leibenluft E, Pine DS, Blair RJ. Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *Am J Psychiatry* 2008;165(6):712–720. [PubMed: 18281412]
18. Rubia K, Halari R, Smith AB, Mohammed M, Scott S, Giampietro V, Taylor E, Brammer MJ. Dissociated functional brain abnormalities of inhibition in boys with pure conduct disorder and in boys with pure attention deficit hyperactivity disorder. *Am J Psychiatry* 2008;165(7):889–897. [PubMed: 18413706] published online ahead of print April 15, 2008
19. Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K, Cook EH Jr. Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry* 2004;161(9):1698–1700. [PubMed: 15337662]
20. Mick E, Kim JW, Biederman J, Wozniak J, Wilens T, Spencer T, Smoller JW, Faraone SV. Family based association study of pediatric bipolar disorder and the dopamine transporter gene (SLC6A3). *Am J Med Genet B Neuropsychiatr Genet*. 10.1002/ajmg.b.30745 published online ahead of print March 24, 2008
21. Rutter M. Gene-environment interdependence. *Dev Sci* 2007;10(1):12–18. [PubMed: 17181693]
22. Pfeifer JC, DelBello MP, Welge J, Adler CM, Strakowski SM. Meta-Analysis of amygdala volumes in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. in press
23. Bearden CE, Soares JC, Klunder AD, Nicoletti M, Dierschke N, Hayashi KM, Narr KL, Brambilla P, Sassi RB, Axelson D, Ryan N, Birmaher B, Thompson PM. Three-dimensional mapping of hippocampal anatomy in adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2008;47(5):515–525. [PubMed: 18356767]

24. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. *Am J Med Genet C Semin Med Genet* 2003;123C(1):48–58. [PubMed: 14601036]
25. Braff DL, Freedman R, Schork NJ, Gottesman II. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophr Bull* 2007;33(1):21–32. [PubMed: 17088422]
26. Hill SK, Harris MS, Herbener ES, Pavuluri M, Sweeney JA. Neurocognitive allied phenotypes for schizophrenia and bipolar disorder. *Schizophr Bull* 2008;24(4):743–759. [PubMed: 18448479] published online ahead of print April 29, 2008
27. Klimes-Dougan B, Ronsaville D, Wiggs EA, Martinez PE. Neuropsychological functioning in adolescent children of mothers with a history of bipolar or major depressive disorders. *Biol Psychiatry* 2006;60(9):957–965. [PubMed: 16934765]
28. Gotlib IH, Traill SK, Montoya RL, Joormann J, Chang K. Attention and memory biases in the offspring of parents with bipolar disorder: indications from a pilot study. *J Child Psychol Psychiatry* 2005;46(1):84–93. [PubMed: 15660646]
29. Brotman MA, Guyer AE, Lawson ES, Horsey SE, Rich BA, Dickstein DP, Pine DS, Leibenluft E. Facial emotion labeling deficits in children and adolescents at risk for bipolar disorder. *Am J Psychiatry* 2008;165(3):385–389. [PubMed: 18245180]
30. Ladouceur CD, Almeida JR, Birmaher B, Axelson DA, Nau S, Kalas C, Monk K, Kupfer DJ, Phillips ML. Subcortical gray matter volume abnormalities in healthy bipolar offspring: potential neuroanatomical risk marker for bipolar disorder? *J Am Acad Child Adolesc Psychiatry* 2008;47(5):532–539. [PubMed: 18356765]
31. Singh MK, Delbello MP, Adler CM, Stanford KE, Strakowski SM. Neuroanatomical characterization of child offspring of bipolar parents. *J Am Acad Child Adolesc Psychiatry* 2008;47(5):526–531. [PubMed: 18356766]