

2009-02-24

AACAP 2006 Research Forum--Advancing research in early-onset bipolar disorder: barriers and suggestions

Gabrielle A. Carlson
SUNY Stonybrook

Et al.

Let us know how access to this document benefits you.

Follow this and additional works at: https://escholarship.umassmed.edu/psych_pp



Part of the [Psychiatry Commons](#)

Repository Citation

Carlson GA, Findling RL, Post RM, Birmaher B, Blumberg HP, Correll C, DelBello MP, Fristad M, Frazier JA, Hammen C, Hinshaw SP, Kowatch R, Leibenluft E, Meyer SE, Pavuluri MN, Wagner KD, Tohen M. (2009). AACAP 2006 Research Forum--Advancing research in early-onset bipolar disorder: barriers and suggestions. *Psychiatry Publications*. <https://doi.org/10.1089/cap.2008.100>. Retrieved from https://escholarship.umassmed.edu/psych_pp/429

This material is brought to you by eScholarship@UMassChan. It has been accepted for inclusion in Psychiatry Publications by an authorized administrator of eScholarship@UMassChan. For more information, please contact Lisa.Palmer@umassmed.edu.

AACAP 2006 Research Forum—Advancing Research in Early-Onset Bipolar Disorder: Barriers and Suggestions

Gabrielle A. Carlson, M.D.,¹ Robert L. Findling, M.D.,² Robert M. Post, M.D.,³
Boris Birmaher, M.D.,⁴ Hilary P. Blumberg, M.D.,⁵ Christoph Correll, M.D.,⁶
Melissa P. DelBello, M.D.,⁷ Mary Fristad, Ph.D.,⁸ Jean Frazier, M.D.,⁹ Constance Hammen, Ph.D.,¹⁰
Stephen P. Hinshaw, Ph.D.,¹¹ Robert Kowatch, M.D., Ph.D.,¹² Ellen Leibenluft, M.D.,¹³
Stephanie E. Meyer, Ph.D.,¹⁴ Mani N. Pavuluri M.D.,¹⁵
Karen Dineen Wagner, M.D., Ph.D.,¹⁶ and Mauricio Tohen, M.D., Dr.P.H.¹⁷

Abstract

Objective: The 2006 Research Forum addressed the goal of formulating a research agenda for early-onset bipolar disorder (EOBP) and improving outcome by understanding the risk and protective factors that contribute to its severity and chronicity.

Method: Five work groups outlined barriers and research gaps in EOBP genetics, neuroimaging, prodromes, psychosocial factors, and pharmacotherapy.

Results: There was agreement that the lack of consensus on the definition and diagnosis of EOBP is the primary barrier to advancing research in BP in children and adolescents. Related issues included: the difficulties in managing co-morbidity both statistically and clinically; acquiring adequate sample sizes to study the genetics, biology, and treatment; understanding the EOBP's developmental aspects; and identifying environmental mediators and moderators of risk and protection. Similarly, both psychosocial and medication treatment strategies for children with BP are hamstrung by diagnostic issues. To advance the research in EOBP, both training and funding mechanisms need to be developed with these issues in mind.

Conclusions: EOBP constitutes a significant public health concern. Barriers are significant but identifiable and thus are not insurmountable. To advance the understanding of EOBP, the field must be committed to resolving diagnostic and assessment issues. Once achieved, with adequate personnel and funding resources, research into the field of EOBP will doubtless be advanced at a rapid pace.

¹Department of Child and Adolescent Psychiatry, Stony Brook University School of Medicine, Stony Brook, New York.

²Department of Psychiatry, University Hospitals Case Medical Center, Cleveland, Ohio.

³Department of Psychiatry, George Washington University, Bethesda, Maryland.

⁴Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

⁵Departments of Psychiatry and Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.

⁶Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, New York.

⁷Division of Bipolar Disorders Research, University of Cincinnati College of Medicine, Cincinnati, Ohio.

⁸Department of Psychology, The Ohio State University, Columbus, Ohio.

⁹Department of Psychiatry, UMASS Medical School, Worcester, Massachusetts.

¹⁰Department of Psychology, University of California, Los Angeles, Los Angeles, California.

¹¹Department of Psychology, University of California Berkeley, Berkeley, California.

¹²Department of Psychiatry, University of Cincinnati Medical Center, Cincinnati, Ohio.

¹³Unit on Affective Disorders/Pediatrics and Developmental Neuropsychiatry Branch, Mood and Anxiety Program, National Institute of Mental Health, Bethesda, Maryland.

¹⁴Division of Child and Adolescent Psychiatry, Cedars-Sinai Medical Center, Los Angeles, California.

¹⁵Department of Psychiatry, University of Illinois at Chicago, Chicago, Illinois.

¹⁶Department of Child and Adolescent Psychiatry, University of Texas, Medical Branch at Galveston, Galveston, Texas.

¹⁷Eli Lilly and Company, Indianapolis, Indiana.

Introduction

THE MAIN OBJECTIVE of the American Academy of Child and Adolescent Psychiatry's Research Forum is to drive the research policy agenda for child and adolescent psychiatry. The 2006 Research Forum was presented with the goal of addressing a research agenda for bipolar disorder (BP) in youths, emphasizing how to improve outcome by understanding the risk and protective factors that contribute to its severity and chronicity.

By all recent accounts, child- and young adolescent-onset bipolar spectrum disorder is a significantly impairing condition that severely disrupts the lives of those afflicted and their families (Pavuluri et al. 2005). Although research on this subject has increased enormously in recent years, we are a long way from knowing how to prevent BP, and our treatments have modest effects at best (see Goodwin and Jamison 2007, pp. 907ff for review). Unfortunately, goals such as treatment and prevention are dependent upon first understanding how to identify cases to be studied. Thus, the primary goal of the research agenda is to refine the multiple definitions of child- and adolescent-onset BP that have been reported in the literature. Clarifying how to identify, describe, assess, and diagnose cases of early-onset bipolar disorder (EOBP) will greatly enhance our ability to meet the rest of the research agenda.

As it was the intention of the forum that lessons about risk factors, co-morbidity, intervention, and prevention may shed light on strategies for research in EOBP, the committee spent a good deal of time reviewing the literature on risk factors, developmental course, and treatments in conditions that often co-occur in children with early-onset BP (e.g., attention-deficit/hyperactivity disorder [ADHD], oppositional defiant disorder [ODD], and major depressive disorder [MDD]). In addition, the committee reviewed methods of developmental, genetic, and neuroimaging studies of these other disorders, again to determine if useful methods, approaches, and strategies could be used to study the children who suffer the complex psychopathology described as EOBP.

Thus, after a review of what is known about BP in youth, what is known about risk and protective factors in ADHD, ODD, and MDD, and what has been done in genetics and neuroimaging in other disorders, the work groups divided up to develop a strategy on how best to advance the field of study of EOBP.

Methods

Five workgroups were charged with identifying hurdles in important domains to be surmounted so that research on the etiology and prevention of EOBP can be conducted. These domains were: genetics (because of the high heritability of the disorder), neuroimaging (because of its promise of providing insights into the biology of the illness), pharmacotherapy (because of its importance to intervention), prodromes (because of the need to understand very early manifestations of illness and the potential for prevention), and psychosocial factors (because of their impact on illness emergence, persistence and treatment response). Recommendations were also solicited.

Results

There were many overlaps to the perceived barriers interfering with research progress. These overlaps and our re-

commendations have been summarized and synthesized below and in the discussion.

Topic #1: Definition and assessment of BP

The biggest and most consistently agreed upon barrier for progress in research on BP in children and adolescents remains the lack of consensus regarding the definition, ascertainment, and even the name of the disorder (Goodwin and Jamison 2007). There is increasing agreement that EOBP exists. The current debate focuses on how frequently it occurs, and whether bipolar spectrum disorders are the appropriate diagnostic home for seriously impaired children who have severe aggression, problems with hyperactivity, impulsivity and inattention, and mood instability. There is disagreement about whether these mood-dysregulated children meet narrow *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) criteria or would meet narrow criteria if criteria were modified, if children have a particular bipolar subtype, or they have one of many conditions that may present with aggression, inattention and mood instability. We have arrived at the controversy for several reasons: (1) DSM favored cross-sectional symptoms over history (Andreassen 2007); (2) neither insurers, the Food and Drug Administration (FDA) (for treatment studies) nor funding agencies want to contend with diagnostic ambiguity; (3) DSM-created co-morbidity but not a way to re-assemble multiple disorders to define subgroups of children; (4) impulsive, affective aggression has been difficult to classify (Connor 2002). Reframed as mood instability, it is no less complicated. Unfortunately, fitting what is likely a multitude of childhood disorders into one diagnostic category originally developed for the study of adult BP remains unsatisfactory at best and destructive at worst. It is destructive both because we do not know which children are being described and thus do not know how to understand research findings, and because the valid scientific questions that have arisen have been framed in ways that cast doubt on the entire profession.

1. **Barriers.** Barriers begin with lack of agreement about how to name children being described in publications. Inconsistently referred to as pediatric or juvenile BP, juvenile or pediatric mania, prepubertal and pubertal BP, or narrow/intermediate/broad phenotype, these names may or may not refer to the same exact condition, and may or may not refer to children with more generic mood dysregulation. For consistency, we will use the term EOBP to refer to onset of mania at ≤ 18 years, and very-early-onset (VEOBP) to onset of mania at ≤ 12 years of age. The term "bipolar" may refer to the entire spectrum, so some studies include BP I, II, and not otherwise specified (NOS), or to the acute manic episode itself. Studies do not always clarify if subjects are acutely ill at the time of assessment, manic or hypomanic (a severity dimension), or if lifetime mania is being ascertained while the patient is euthymic or depressed. The distinction between levels of severity or between current and lifetime mania is important to understanding results of biological studies. For instance, severity of illness impacts treatment outcome in ADHD (Hinshaw 2007) and depression (Curry et al. 2006).

2. **Operationalizing criteria.** Although structured or semistructured interviews are used to establish diagnoses,

researchers differ on how they elicit, assess, characterize, and count criteria (Youngstrom et al. 2006). The degree to which these decisions influence their sample selection and ultimate findings is unclear (Galanter et al. 2008). There is, as yet, no “right or wrong” about the various approaches—only that the end result means that sample A may sound superficially like sample B (i.e., both have “BP”), but may contain people who would not be included in sample B.

Classic manic depression, as described by Goodwin and Jamison (2007) (pp. 29–87) is apparently very uncommon in VEOBP (Harrington and Myatt 2003). As the boundaries of BP have broadened, the symptoms and diagnosis have become more common in both youth and adults (Biederman et al. 2004; Hirschfeld and Vornik 2004).

Investigators disagree about the necessity for euphoria or grandiosity to be present (Geller et al. 2002; Leibenluft et al. 2003). Some feel that severe irritability/explosiveness is the defining feature of VEOBP (Mick et al. 2005). Research on the taxonomy of irritability is clearly needed. It is important to distinguish the level of reactivity inherent in the definition of irritability from the subsequent response. The development of psychometrically valid scales for irritability separate from those designed to measure aggression and mania would facilitate etiologic as well as treatment research (Jensen et al. 2007).

3. Episodes. In acute mania, the relative rapidity of change from premorbid functioning helps make clear an episode’s onset. Return to a premorbid level of functioning with very mild or no symptoms defines the offset. Without a clear onset and offset, disentangling episode onset from developmental shifts (onset of particularly terrible twos or threes, stressful transitions to school in a child with other problems), or defining “stable baseline” in someone who is still very young may be difficult. There are several questions that arise about episodes. One is how long symptoms need to co-occur to have predictive validity for future BP. Some young people with classic manic symptoms that may last for less than 4 days and subsequently develop full BP I or BP II (Birmaher et al. submitted). Another is whether EOBP is exclusively an episodic illness (narrow-phenotype BP) or whether it also encompasses nonepisodic deficits in emotion regulation (e.g., severe mood dysregulation). The intramural National Institute of Mental Health (NIMH) bipolar program is attempting to address that question (Leibenluft et al. 2003) with longitudinal studies (e.g., Brotman et al. 2006), family history research (e.g., Brotman et al. 2007), and specific studies of brain mechanisms (e.g., studies of the impact of reward, punishment, and frustration on attention in pediatric BP) (Rich et al. 2007).

4. Pervasiveness of symptoms. Both DSM-III/IV and the International Statistical Classification of Diseases, 10th revision (ICD 10) recognize the need for ADHD symptoms or some impairment to be present in more than one setting; ICD 10 requires the full disorder in two settings. There is no such consideration for mania because the symptoms were developed from pervasively ill adults, usually hospitalized (Goodwin and Jamison 2007, pp. 89–115). A condition that occurs in only one setting likely differs from one that is pervasive. A child with less severe hypomania may be more situationally contained than one with psychotic mania. A different disorder, anxiety, may cause a child to behave well at

school because s/he is self-conscious and be subsequently symptomatic at home where s/he is comfortable. The implications of manic symptoms in only one setting clearly need further research to determine, among other things, whether inconsistent observations across settings rule out the diagnosis of mania or imply a less severe condition.

5. Information variance. Parents are always interviewed, but some researchers only interview children over age 12; others interview all youths. However, it is not always stated whether criteria are met by symptoms from parent, from child, some from each (the “OR” rule), requires both parent and child to agree (the “AND” rule), or uses parent-only information if there is disagreement. Decisions about informants need more than a simplistic “and/or” rule (Kraemer et al. 2003). In genetic studies, heritability estimates in children may change depending on informant source (Thapar and Rice 2006).

6. Long-term stability of diagnosis in VEOBP. If a lifetime manic or hypomanic episode is endorsed at one time and not another, it is assumed that its presence is the accurate report. Yet both false-positive and false-negative reports are problematic. Mild episodes may be missed (Kendler et al. 2001), but recall may not accurately distinguish manic symptoms from co-morbid symptoms of anxiety, agitation, or ADHD. Although there are adult studies of longitudinal reliability of major depression (Kendler et al. 2001) and psychosis (Schwartz et al. 2000), diagnosis and stability of diagnosis of mania or hypomania over more than a year or two has barely been explored in adults (Fraguas et al. 2008; Ruggero et al., 2009) let alone in children and adolescents. A further potential confound occurs when informants change from parent to offspring.

Topic #2: Managing co-morbidity

Co-morbidity, whether it represents true co-occurrence of disorder or is a sign of illness severity, complicates treatment and outcome (Carlson et al. 2002; Consoli et al. 2007). For EOBP, common co-morbid disorders include ADHD and ODD/conduct disorder (CD), anxiety disorders, and, in teens, substance abuse. Other possible co-morbidities, like autism spectrum disorders, or disorders co-morbid with ADHD, like learning and language disorders, are not usually assessed (Cohen et al. 1989; Carlson and Meyer 2006). Some conditions that may occur, like those involving sensory integration or social skills deficits, have no DSM label and therefore have no way of even being coded. Co-morbidities, whether identified or not, undoubtedly affect outcome (Carlson et al. 2002; Lahey 2008).

Handling co-morbidities is challenging. Ascertaining the presence of another condition is addressed differently by different research groups. For instance, some researchers may count the same symptom (e.g., hyperactivity) toward both ADHD and mania. Others specify that hyperactivity can count toward the diagnosis of mania only if it begins (or worsens over a baseline level) at the same time as the change in mood. Another point of inconsistency between research groups is whether to even consider a condition co-morbid unless it is present only when the youth is euthymic.

Inclusion of a co-morbid disorder requires decisions about how to account in the data analysis not just for the specific

disorder but also for the cumulative impact and increased severity that co-morbidities confer on outcome in general and treatment in particular (Curry et al. 2006; Consoli et al. 2007; Hinshaw 2007). In addition, each co-morbidity has its own neurobiology, genetics, and level of severity. However, exclusion of co-morbid disorders limits the ecological validity of studies, not to mention the sheer difficulty of finding children without a comorbid disorder.

Topic #3: Acquisition of adequate sample sizes

A barrier to understanding EOBP, its neuroscience (including imaging and neuropsychological studies), treatment (psychopharmacologic and psychosocial), and outcome is acquiring adequate sample size. The narrower the definition of EOBP that is used, the longer it takes to collect a reasonable number of patients to study. However, in the absence of a good sample description, unacknowledged heterogeneity is introduced. Depending on the nature of the study, this is more or less important. Certain phenotypes used in genetic studies (e.g., the Child Behavior Checklist–juvenile/pediatric bipolar phenotype) (Biederman et al. 1995) lend themselves to easy definition and identification and have yielded important findings in terms of heritability (Althoff et al. 2006), but relevance to BP has not been consistently demonstrated (Meyer et al. 2008; Volk and Todd 2007).

Topic #4: Standardization of measures across sites

One approach to collecting large samples is the performance of multisite studies. These raise important issues with regard to standardizing measures across sites. Reliability of interviews and rating scales is possible within and across groups, and some important multisite studies are already underway. Especially careful consideration needs to be given in the design of multi-site neuroimaging studies. There are numerous potential sources of variability across sites that need to be taken into account which include magnetic resonance imaging (MRI) data acquisition (e.g., scanner manufacturer, field strength, sequence specifications), preprocessing (e.g., preprocessing software, parameters, normalization templates), analysis tools (e.g., investigator preference for use of widely available software such as statistical parametric mapping [SPM], <http://www.fil.ion.ucl.ac.uk/spm/>; FSL, <http://www.fmrib.ox.ac.uk/fsl/>; or Freesurfer, <http://www.nmr.mgh.harvard.edu/freesurfer/>, or site-specific home-grown software) and performance of software operators (e.g. in anatomical determinations such as in region-of-interest delineations). Testing of reliability across sites is recommended but is labor intensive.

Topic #5: Developmental psychopathology

Understanding symptoms of EOBP requires understanding the development of: (1) emotion regulation (which is relevant to our understanding of mood lability, mood “swings”, pathological euphoria and irritability) (Cole and Hall 2008); (2) reality testing (which is relevant to the concept of grandiosity) (Caplan et al. 2000); (3) temperament (which, like comorbidity, is likely to interact with, and depending on the temperament, worsen the disorder) (Rutter et al. 2006; Klein et al. 2008; Lahey 2008); (4) social cognition and language development that is, receptive, expressive and pragmatic

(which impacts both outcome) (Lahey 2008) and accuracy of reporting symptoms that require meta-cognitive ability.

Imaging researchers are increasingly incorporating neurodevelopmental perspectives into studies of BP. These have led to recent advances in the identification of limbic regions involved in EOBP, and research designed to identify continuities and discontinuities in the involvement of limbic circuitry in pediatric and adult presentations of BP (DelBello et al. 2004; Frazier et al. 2005; Blumberg et al. 2006; Rich et al. 2006; Pavuluri et al. 2007). Puberty plays an important role in brain development (Blakemore and Choudhury 2006) and is associated with a dramatic increase in rates of depression and schizophrenia; however, there has been a paucity of research investigating the role of puberty in BP. Future investigations that address peripubertal brain changes and neurodevelopmental trajectories in girls and boys associated with the emergence of bipolar symptoms may be pivotal in our understanding of the pathophysiology of the disorder.

Topic #6: Identifying children at risk and the need for longitudinal studies

Affective and behavioral symptoms in children at familial risk for BP may portend significantly impairing BP I (Lapalme et al. 1997; Hillegers et al. 2005; Meyer et al. 2006; Duffy et al. 2007). However, these nonspecific symptoms may be on the bipolar spectrum, harbingers of other behavior disorders separate from or co-morbid with BP, or transient developmental deviations from the norm. As with most dimensions, the boundaries between the upper limit of normal and early disorder are muddy. Moreover, if schizophrenia is any example, many years elapse between the onset of nonspecific behavioral disturbance, development of idiosyncratic thoughts and perceptions, and ultimate psychosis (Maziade et al. 1996). The relationship of behavioral symptoms and the eventual development of psychosis are much more easily demonstrated retrospectively than prospectively. To delineate a bipolar prodrome clearly, then, a key first step is agreeing on the actual disorder, then on what its prodrome is, then who among children at risk has the prodrome, and finally who of these progresses to final disorder, versus remits, versus remains subthreshold but symptomatic (Correll et al. 2007). To do that, longitudinal studies of high-risk youth will be necessary.

Topic #7: Psychosocial risk factors

Concepts from developmental psychopathology (Cicchetti 1984; Rutter et al. 2006) have drawn increasing attention to the early origins of risk for depression, including studies of children of depressed parents. An emphasis on the unfolding of critical developmental tasks, the interplay between organism and environment, and the effects of earlier adaptations and dysfunctions on later development, have informed our understanding of recurrent depression as largely a disorder of early onset accompanied by multiple failures of adaptive learning or maladaptive transactions among personal biopsychosocial vulnerabilities and environmental adversities (Costello et al. 2002; Kendler et al. 2006). Earlier adaptive difficulties portend later cognitive, school, and social maladjustment, typically leading to greater levels of symptomatology, in a pernicious cascade of interacting factors including, possibly, poorer response to treatment (Curry et al. 2006).

Similarly, there are suggestions that life events, cognitive vulnerability, the cognitive vulnerability-stress combination, poor parenting, and maltreatment play a role in the onset and course of EOBP (Alloy et al. 2005). Low socioeconomic status (SES), stressful life events, cognitive style, negative, hostile parenting as reflected in low maternal warmth, poor social supports, parent divorce and conflict, low levels of family cohesion and organization, increased family conflict, and physical and sexual abuse have all been identified as risk factors for development or exacerbation of EOBP (Leverich et al. 2002; Tillman et al. 2003; Alloy et al. 2005; Birmaher et al. 2006; Kim et al. 2007). Other negative course indicators include rapid cycling, suicidal behavior, and high rates of co-morbidity (Leverich et al. 2002). Insecure attachment is a risk factor for emotional dysregulation and externalizing disorders among offspring of parents with BP (Zahn-Waxler et al. 1988; Speltz et al. 1999; Shaw et al. 2001). Prenatal risk factors, including exposure to prescribed medications (Pavuluri et al. 2006) and nonprescribed substances (O'Connor et al. 2002), may be important predictors of EOBP.

Although there has been increased interest in nongenetic contributions to BP, much more work is needed to understand complex environmental risk and protective factors and their interaction with genetic risk (Meyer et al. 2004; Moffitt et al. 2005). Multiinformant measures and methodology that allow disentangling the impact of various psychosocial measures on severity and co-morbidity versus a specific impact on BP will be needed.

Topic #8: Genetics

Both BP and its age of onset appear to be influenced by genetics (Faraone et al. 2004; Althoff et al. 2005), and while considerable research has focused on genetic contributions to the adult-onset phenotype, little is known about the genetic, environmental, gene-gene, or gene-environment interaction influences on EOBP. Behavioral genetic data and molecular genetic studies to date support both genetic and environmental contributions to EOBP (Geller et al. 2006). BP is familial (Geller et al. 2006; Hirshfeld-Becker et al. 2006; Brotman et al. 2007; Rende et al. 2007), and considerable research has focused on genetic risk factors for BP in adults (Hayden and Nurnberger 2006). Far less genetic research has been done on EOBP. Of the strategies available to the psychiatric geneticist (family studies, twin studies, adoption studies, whole genome association, methylation, or copy number variation, linkage, and simple association studies), the majority of studies to date have been family studies. These reveal that early-onset psychopathology (ADHD, ODD, CD, MDD and EOBP) is more common in offspring of parents with BP. It has also been shown that some but not most children with suggestive bipolar symptoms grow up to have adult BP, although far more have a wide variety of other psychopathologies (Meyer et al. 2008). Twin studies of 'markers' of EOBP indicate that the broadly defined condition is different from other common psychopathologies (Hudziak et al. 2005). Of the four molecular genetic studies in EOBP probands, one found an association with the *val66* allele of the brain-derived neurotrophic factor (BDNF) gene (Geller et al. 2004a), while another found evidence of linkage to chromosome 9q34 (Faraone et al. 2006).

Hampering progress in genetics, not surprisingly, is the lack of a clearly defined, replicable phenotype. Certain forms

of genetic studies require very large sample sizes (ideally, in the thousands), thus multisite studies are essential and will require common criteria and assessment techniques, so that large samples can be collected from multiple sites.

Topic #9: Need for treatment studies and predictors of response

Data suggest that, compared to those in adults, episodes of mania and depression in youth are more protracted, and mood is less stable even within an episode of mania or depression, both of which contribute to poor prognosis (Geller et al. 2004b; Birmaher et al. 2006). High rates of co-morbidity with conditions that themselves have poor prognoses (e.g., ADHD with co-morbid oppositional-defiant or conduct disorder) confer a poor outcome (Lahey 2008). We need more effective medications and treatment strategies to treat mania and depression and prevent relapse to forestall this outcome.

Difficulty acquiring large enough homogeneous samples to demonstrate efficacy and examine response predictor as well as lack of a uniform approach to co-morbidity are problems. Negative publicity surrounding clinical research in general hampers public support. Retention in short-term pediatric trials has been adequate, but could be better. Retention in longer-term treatment trials is perhaps understandably worse.

There are substantive gaps between the ideal development of a drug as a treatment for a condition and what currently is occurring in the field of EOBP, including:

1. Determining the appropriate doses of medication: This requires knowledge of the biodisposition of a drug (Kearns et al. 2003). Failure to determine appropriate dosing strategies adequately can influence the outcome of medication treatments (Findling 2004).
2. Identifying a therapeutic window from minimally effective to maximally tolerated: This is generally accomplished by performing prospective studies in youth with the disease entity in question, that examine safety and tolerability of different dosing strategies. These studies must identify the right starting dose, the rate of upward dose titration (if it is necessary to achieve a target dose), and the therapeutic dose range. Unfortunately, these fundamental pharmacological parameters are oftentimes not identified in youth prior to the conduct of definitive placebo controlled trials.
3. The results of safety and efficacy studies in youth are not available to inform their treatment until several years after they are marketed for adults.
4. Many youths will receive drug therapy for a protracted period of time. Studies that examine these agents' long-term safety and effectiveness need to be conducted.

There are other key areas of unmet need for treatment research in general:

1. There are key unstudied patient populations, including children younger than 10 and patients who have bipolar spectrum conditions.

2. Patients with EOBP with substantive co-morbidities often are not enrolled in clinical trials. Moreover, the co-morbid conditions themselves need treatment.

3. The sheer number of family/environment/developmental factors important in other disorders means that nonmedication strategies will be needed and need to be studied along with medication interventions (Pavuluri et al. 2004; Fristad 2006; Miklowitz 2008). In adults with BP, these controlled nonpharmacologic interventions are demonstrating success in increasing medication adherence and increasing time before the next relapse.

4. Both the Multimodal Treatment Study of Children with ADHD (MTA) and Treatment for Adolescents with Depression Study (TADS) trials found important moderators and mediators of favorable treatment response (Curry et al. 2006; Hinshaw 2007). In essence, these consisted basically of less severe and less complicated illness and better-functioning families. These are also predictors of better outcomes in EOBP in general, as noted earlier, but should be examined with respect to treatment response as well.

5. Pharmacogenomic studies that can examine genetic mediators of both treatment response and adverse events are needed.

6. Incorporating neuroimaging techniques into treatment research may be able to provide useful insights (DelBello et al. 2006; Moore et al. 2007). The effects of interventions on the brain can be evaluated using several neuroimaging approaches: (a) comparing subjects taking medications to those who are not; (b) combining neuroimaging studies with treatment trials to assess neurobiological predictors of individual treatment response; and (c) assessing children treated acutely and longitudinally to ascertain immediate and chronic medication effects.

Topic #10: Lack of research funding and people to do the research

Every condition has advocates clamoring for more government research dollars. To advance the needed research agenda, EOBP will need this as well. There is a shortage of people equipped to do the research. Focused and dedicated support from stakeholders, such as those who have worked successfully in autism research, is needed for this condition.

Recommendations

1. Adequate characterization of the heterogeneous group of children who are significantly impaired with mood related problems might be achieved in several ways:

(a) Convening one or several reconciliation meetings with the goal of arriving at inclusive definitions and assessment techniques, information to be solicited beyond symptom criteria, and from whom to obtain the information. In conjunction with this, a glossary would be compiled that would clearly operationalize symptoms such as irritability, euphoria,

and grandiosity, which can be difficult to elicit accurately and diagnose in a developmentally and gender-sensitive fashion.

A reconciliation approach would allow all research groups to understand where different phenotypic definitions fit into the broader picture. What has complicated work up to now is that investigators say they are using the same criteria, methods, and terms but use and define them differently (Youngstrom et al. 2006).

(b) In addition, research groups would provide information, perhaps using the "article-plus" format, or in a publicly available website, in much greater detail than is usually described in scientific journals about the specific methods employed in their studies. This would entail not only worded descriptions but also taped material to disclose how certain patient responses to questions were interpreted or how certain diagnostic decisions were made. This could facilitate the interpretation of scientific results generated from different research groups and could help provide insights regarding why between-site differences in study results sometimes occur. The difference between a reconciliation and a consensus conference is that differences are highlighted and allowed in the former as long as they are operationalized and identified.

(c) When significant differences in conceptualization of ADHD were found between the United States and United Kingdom, a study was organized using case material rated by experts in both countries to determine where the source of invariance arose (Prendergast et al. 1988). A recent, limited version of that study done on children with manic symptoms indicated similar discrepancies in how information was interpreted (Dubicka et al. 2008). A more extensive study to illustrate discrepancies and refine ways of eliminating them might be useful.

2. The need for multisite/collaborative endeavors. Multisite studies can facilitate enrollment of larger sample sizes than are generally feasible in single-site studies, increasing statistical power. However, harmonization of ascertainment and assessment is mandatory for multisite studies. Formation of a treatment outcome network for EOBP similar to the adult Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BP program) (Sachs et al. 2003) is another approach that would allow collection of longitudinal, naturalistic data about effectiveness and tolerability of treatment.

3. Sample selection. Recognizing the heterogeneity of children with mood dysregulation, it would be informative to include for longitudinal study a group of youth with mood dysregulation and manic symptomatology and patients demonstrating specific expressions of bipolarity. Such a study could clarify how greater or lesser degrees of specificity impact outcome or are affected by development, co-morbidity, and the like.

4. Treatment studies. The FDA has limited industry-sponsored treatment studies to people with definable diagnoses. Studies are needed of children with explosive behavior. One possibility would be to use groups of children with ADHD and co-morbid ODD/CD with levels of explosive behavior similar to that of bipolar spectrum youths to clarify similarities and differences in treatment responses.

Brain imaging and other neurobiological studies, including pharmacogenomic studies, should be added to treatment studies so that preliminary data regarding treatment response and adverse events would be available from those studies as well. Where existing treatment studies have used the same methodology, samples could be combined to increase power and examine response predictors.

5. Genetic studies. Longitudinal twin and sib-pair studies can be used to study potential protective factors (e.g., family cohesion, peer relations) and novel risk factors (e.g., being bullied, birth season). In addition, pathophysiological family studies designed to identify endophenotypes can facilitate molecular genetic studies. Such studies can combine neuroimaging and genetic techniques.

Assuming that some type of nosologic reconciliation can occur, new techniques on large singleton, twin, and family samples can be applied to EOBP. In recent months, whole-genome association, methylation, and copy number variation approaches have yielded exciting results in other complex disorders (diabetes, autism, etc.) and may offer promise in studies of EOBP. Additional strategies, such as the use of monozygotic twin pairs discordant for EOBP and offspring of twin designs, offer added new frontiers for inquiry. Each of these approaches will still depend on a clear taxonomic strategy.

6. Fiscal implications. Studies that include large number of subjects, multiple investigative sites, and longitudinal design will require specifically targeted Requests for Applications (RFAs) as well as new funding mechanisms and initiatives. Training grants to focus specifically on developing more investigators in the field of EOBP will increase the probability that key questions about EOBP may be answered. Combined private and government philanthropy, such as the relatively recently organized annual Pediatric Bipolar Conference, has been helpful in stimulating young investigators.

Given that the extent of bipolar spectrum disorders in adults is upwards of 4% (Merikangas et al. 2007), and that it is an early-onset and genetic disorder, then it is incumbent on us to find ways of diagnosing it early and preventing its progression. It is the hope of the Research Forum contributors that some of the deliberations will facilitate progress toward that end.

Disclosures

Dr. Carlson receives or has received research support, or has acted as an advisor/consultant and/or served as a speaker for Eli Lilly, Otsuka, Bristol-Myers Squibb, GlaxoSmithKline, and Lundbeck. Dr. Findling receives or has received research support, acted as a consultant, and/or served on a speaker's bureau for Abbott, Addrenex, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, Eli Lilly, Neuropharm, Novartis, Organon, Otsuka, Pfizer, Sanofi-Aventis, Sepracore, Shire, Solvay, Supernus Pharmaceuticals, and Wyeth. Dr. Post has been a consultant to and speaker for Abbott, AstraZeneca, Bristol-Myers Squibb, and GlaxoSmithKline. Dr. Birmaher's research is currently funded by the National Institute of Mental Health, and he has participated in forums sponsored by Forest Laboratories, Inc., Shire Pharmaceuticals, JAZZ Pharmaceuticals, Solvay Pharmaceu-

ticals, Inc., and Abcomm, Inc. Dr. Blumberg has acted as a consultant to Pfizer. Dr. Correll has been a consultant to or has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Otsuka, Pfizer, Supernus, and Vanda, and has served on the speaker's bureau of AstraZeneca, Bristol-Myers Squibb/Otsuka, and Pfizer. Dr. DelBello receives or has received research support from, served on a lecture bureau for, or has acted as a consultant/advisor or received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, Kappa Clinical, Martek, medical communications media, NARSAD, NIAAA, NIDA, NIMH, Pfizer, Repligen, Somerset, and Thrasher Foundation. Dr. Frazier receives or has received research support from Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Johnson & Johnson, Neuropharm, Otsuka, and Pfizer. Dr. Kowatch receives or has received research support from, acted as a consultant/advisor to, or served on a speaker's bureau for AstraZeneca, Child Adolescent Bipolar Foundation, Kappa, Medscape, NIMH, NICHD, Physicians Postgraduate Press, and the Stanley Research Foundation. Dr. Pavuluri's work is supported by NIH, NICHD, NARSAD, Dana Foundation, Colbeth Foundation, Abbott Pharmaceuticals (study medication), and Janssen Research Foundation (study medication); she has received grant support from GlaxoSmithKline and has served as a speaker for AstraZeneca in the past 3 years. Dr. Wagner has received research support from NIMH and has acted as a consultant to Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, Janssen, Jazz Pharmaceuticals, Novartis, Otsuka, Pfizer, and Solvay. Dr. Tohen is an employee of and stockholder for Eli Lilly & Co. The other authors have no financial ties or conflicts to disclose.

References

- Alloy LB, Abramson LY, Urosevic S, Walshaw PD, Nusslock R, Nereen AM: The psychosocial context of bipolar disorder: environmental, cognitive, and developmental risk factors. *Clin Psychol Rev* 25:1043–1075, 2005.
- Althoff RR, Faraone SV, Rettew DC, Morley CP, Hudziak JJ: Family, twin, adoption, and molecular genetic studies of juvenile bipolar disorder. *Bipolar Disord* 6:598–609, 2005.
- Althoff RR, Rettew DC, Faraone SV, Boomsma DI, Hudziak JJ: Latent class analysis shows strong heritability of the child behavior checklist-juvenile bipolar phenotype. *Biol Psychiatry* 60:903–911, 2006.
- American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV). Washington (DC): American Psychiatric Association, 1994.
- Andreasen NC: DSM and the death of phenomenology in America: An example of unintended consequences. *Schizophr Bull.* 33:108–112, 2007.
- Biederman J, Wozniak J, Kiely K, Ablon S, Faraone S, Mick E, Mundy E, Kraus I: CBCL clinical studies discriminate prepubertal children with structured interview-derived diagnosis of mania from those with ADHD. *J Am Acad Child Adolesc Psychiatry* 34:464–471, 1995.
- Biederman J, Mick E, Faraone SV, Van Patten S, Burbach M, Wozniak J: A prospective follow-up study of pediatric bipolar disorder in boys with attention-deficit/hyperactivity disorder. *J Affect Disord* 82 (Suppl):S17–S23, 2004.
- 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* 63:175–183, 2006.
- Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, Houck P, Iyengar S, Kim E, Yen S, Esposito-Smythers C, Goldstein T, Ryan N, Keller M: Four-year longitudinal course of pediatric bipolar spectrum disorder. *Am J Psychiatry* (submitted).
- Blakemore SJ, Choudhury S: Development of the adolescent brain: Implications for executive function and social cognition. *J Child Psychol Psychiatry* 47:296–312, 2006.
- Blumberg HP, Krystal JH, Bansal R, Martin A, Dziura J, Durkin K, Martin L, Gerard E, Charney DS, Peterson BS: Age, rapid-cycling, and pharmacotherapy effects on ventral prefrontal cortex in bipolar disorder: A cross-sectional study. *Biol Psychiatry* 59:611–618, 2006.
- 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 dysregulation in children. *Biol Psychiatry*. 60:991–997, 2006.
- Brotman MA, Kassem L, 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* 164:1238–1241, 2007.
- Caplan R, Guthrie D, Tang B, Komo S, Asarnow RF: Thought disorder in childhood schizophrenia: Replication and update of concept. *J Am Acad Child Adolesc Psychiatry* 39:771–778, 2000.
- Carlson GA, Meyer SE: Phenomenology and diagnosis of bipolar disorder in children, adolescents, and adults: Complexities and developmental issues. *Dev Psychopathol* 18:939–969, 2006.
- Carlson GA, Bromet EJ, Driessens C, Mojtabai R, Schwartz JE: Age at onset, childhood psychopathology, and 2-year outcome in psychotic bipolar disorder. *Am J Psychiatry* 159:307–309, 2002.
- Cicchetti D: The emergence of developmental psychopathology. *Child Dev* 55:1–7, 1984.
- Cohen NJ, Davine M, Meloche-Kelly M: Prevalence of unsuspected language disorders in a child psychiatric population. *J Am Acad Child Adolesc Psychiatry* 28:107–111, 1989.
- Cole PM, Hall SE: Emotion dysregulation as a risk factor for psychopathology. In: *Child and Adolescent Psychopathology*. Edited by Beauchaine TP, Hinshaw, SP. Hoboken (New Jersey): John Wiley & Sons, 2008, pp 265–300.
- Connor DF: Definitions and subtypes of aggressive behavior. In: *Aggression and Antisocial Behavior in Children And Adolescents*. New York (New York): Guilford Press, 2002, pp 1–27.
- Consoli A, Bouzamondo A, Guilé JM, Lechat P, Cohen D: Comorbidity with ADHD decreases response to pharmacotherapy in children and adolescents with acute mania: Evidence from a metaanalysis. *Can J Psychiatry* 52:323–328, 2007.
- Correll CU, Penzner JB, Lencz T, Auther A, Smith CW, Malhotra AK, Kane JM, Cornblatt BA: Early identification and high-risk strategies for bipolar disorder. *Bipolar Disord* 9:324–338, 2007.
- Costello EJ, Pine D, Hammen C, March JS, Plotsky PM, Weissman MM, Biederman J, Goldsmith HH, Kaufman J, Lewinsohn PM, Hellander M, Hoagwood K, Koretz DS, Nelson CA, Leckman JF: Development and natural history of mood disorders. *Biol Psychiatry* 52:529–542, 2002.
- Curry J, Rohde P, Simons A, Silva S, Vitiello B, Kratochvil C, Reinecke M, Feeny N, Wells K, Pathak S, Weller E, Rosenberg D, Kennard B, Robinis M, Ginsburg G, March J; TADS Team: Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry* 45:1427–1439, 2006.
- DelBello MP, Zimmerman ME, Adler CM, Mills NP, Getz GE, Strakowski SM: Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. *Bipolar Disord* 6:43–52, 2004.
- DelBello MP, Cecil KM, Adler CM, Daniels JP, Strakowski SM: Neurochemical effects of olanzapine in first-hospitalization manic adolescents: A proton magnetic resonance spectroscopy study. *Neuropsychopharmacol* 31:1264–1273, 2006.
- Dubicka B, Carlson GA, Vail A, Harrington R: Prepubertal mania: Diagnostic differences between US and UK clinicians. *Eur Child Adolesc Psychiatry* 17:153–161, 2008.
- Duffy A, Alda M, Crawford L, Milin R, Grof P: The early manifestations of bipolar disorder: A longitudinal prospective study of the offspring of bipolar parents. *Bipolar Disord* 9:828–838, 2007.
- Faraone SV, Glatt SJ, Su J, Tsuang MT: Three potential susceptibility loci shown by a genome-wide scan for regions influencing the age at onset of mania. *Am J Psychiatry* 61:625–630, 2004.
- Faraone SV, Lasky-Su J, Glatt SJ, Van Eerdewegh P, Tsuang MT: Early onset bipolar disorder: Possible linkage to chromosome 9q34. *Bipolar Disord* 8:144–151, 2006.
- Findling RL: The relevance of pharmacokinetic studies of antidepressants. Berlin (Germany), 16th World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP), 2004.
- Fraguas D, de Castro MJ, Medina O, Parellada M, Moreno D, Graell M, Merchán-Naranjo J, Arango C: Does diagnostic classification of early-onset psychosis change over follow-up? *Child Psychiatry Hum Dev* 39:137–145, 2008.
- Frazier JA, Chiu S, Breeze JL, Makris N, Lange N, Kennedy DN, Herbert MR, Bent EK, Koneru VK, Dieterich LE, Hodge SM, Rauch SL, Grant PE, Cohen BM, Seidman LJ, Caviness VS, Biederman J: Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. *Am J Psychiatry* 162:1256–1265, 2005.
- Fristad MA: Psychoeducational treatment for school-aged children with bipolar disorder. *Dev Psychopathol* 18:1289–1306, 2006.
- Galanter C, Goyal P, Jenna L, Fisher P: Sources of Diagnostic Variability in Pediatric Bipolar Disorder Diagnostic Instruments, Cambridge (Massachusetts), Childhood Bipolar Meeting, 2008.
- Geller B, Zimmerman B, Williams M, Delbello MP, Frazier J, Beringer L: Phenomenology of prepubertal and early adolescent bipolar disorder: Examples of elated mood, grandiose behaviors, decreased need for sleep, racing thoughts and hypersexuality. *J Child Adolesc Psychopharmacol* 12:3–9, 2002.
- 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* 161:1698–1700, 2004a.
- Geller B, Tillman R, Craney JL, Bolhofner K: Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry* 161:459–467, 2004b.
- Geller B, Tillman R, Bolhofner K, Zimmerman B, Strauss NA, Kaufmann P: Controlled, blindly rated, direct-interview family study of a prepubertal and early-adolescent bipolar I disorder phenotype: Morbid risk, age at onset, and comorbidity. *Arch Gen Psychiatry* 63:1130–1138, 2006.

- Goodwin FK, Jamison KR: Manic Depressive Illness: Bipolar Disorders and Recurrent Depression, 2nd edition. New York: Oxford University Press, 2007.
- Harrington R, Myatt T: Is preadolescent mania the same condition as adult mania? A British perspective. *Biol Psychiatry* 53:961–969, 2003.
- Hayden EP, Nurnberger JI Jr: Molecular genetics of bipolar disorder. *Genes Brain Behav* 5:85–95, 2006.
- Hillegers MH, Reichart CG, Wals M, Verhulst FC, Ormel J, Nolen WA: Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. *Bipolar Disord* 7:344–350, 2005.
- Hinshaw SP: Moderators and mediators of treatment outcome for youth with ADHD: Understanding for whom and how interventions work. *J Pediatr Psychol* 32:664–675, 2007.
- Hirschfeld RM, Vornik LA: Recognition and diagnosis of bipolar disorder. *J Clin Psychiatry* 65(15 Suppl):S5–S9, 2004.
- Hirshfeld-Becker DR, Biederman J, Henin A, Faraone SV, Dowd ST, De Petrillo LA, Markowitz SM, Rosenbaum JF: Psychopathology in the young offspring of parents with bipolar disorder: A controlled pilot study. *Psychiatry Res* 145:155–167, 2006.
- Hudziak JJ, Althoff RR, Derks EM, Faraone SV, Boomsma DI: Prevalence and genetic architecture of Child Behavior Checklist-juvenile bipolar disorder. *Biol Psychiatry* 58:562–568, 2005.
- Jensen PS, Youngstrom EA, Steiner H, Findling RL, Meyer RE, Malone RP, Carlson GA, Coccato EF, Aman MG, Blair J, Dougherty D, Ferris C, Flynn L, Green E, Hoagwood K, Hutchinson J, Laughren T, Leve LD, Novins DK, Vitiello B: Consensus report on impulsive aggression as a symptom across diagnostic categories in child psychiatry: Implications for medication studies. *J Am Acad Child Adolesc Psychiatry* 46:309–322, 2007.
- Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE: Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med* 349:1157–1167, 2003.
- Kendler KS, Gardner CO, Prescott CA: Are there sex differences in the reliability of a lifetime history of major depression and its predictors? *Psychol Med* 31:617–625, 2001.
- Kendler KS, Gardner CO, Prescott CA: Toward a comprehensive developmental model for major depression in men. *Am J Psychiatry* 163:115–124, 2006.
- Klein DN, Torpey DC, Bufferd SJ: Depressive Disorders. In: *Child and Adolescent Psychopathology*. Edited by Beauchaine TP, Hinshaw SP. Hoboken (New Jersey): John Wiley & Sons, 2008, pp 477–509.
- Kim EY, Miklowitz DJ, Biuckians A, Mullen K: Life stress and the course of early-onset bipolar disorder. *J Affect Disord* 99:37–44, 2007.
- Kraemer HC, Measelle JR, Ablow JC, Essex MJ, Boyce WT, Kupfer DJ: A new approach to integrating data from multiple informants in psychiatric assessment and research: Mixing and matching contexts and perspectives. *Am J Psychiatry* 160:1566–1577, 2003.
- Lahey, B: Oppositional defiant disorder, conduct disorder and juvenile delinquency. In: *Child and Adolescent Psychopathology*. Edited by Beauchaine TP, Hinshaw SP. Hoboken (New Jersey): John Wiley & Sons, 2008, pp 335–369.
- Lapalme M, Hodgins S, LaRoche C: Children of parents with bipolar disorder: A metaanalysis of risk for mental disorders. *Can J Psychiatry* 42:623–631, 1997.
- Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS: Defining clinical phenotypes of juvenile mania. *Am J Psychiatry* 160:430–437, 2003.
- Leverich GS, McElroy SL, Suppes T, Keck PE Jr, Denicoff KD, Nolen WA, Altshuler LL, Rush AJ, Kupka R, Frye MA, Autio KA, Post RM: Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol Psychiatry* 51:288–297, 2002.
- Maziade M, Bouchard S, Gingras N, Charron L, Cardinal A, Roy MA, Gauthier B, Tremblay G, Côté S, Fournier C, Boutin P, Hamel M, Mérette C, Martinez M: Long-term stability of diagnosis and symptom dimensions in a systematic sample of patients with onset of schizophrenia in childhood and early adolescence. II: Postnegative distinction and childhood predictors of adult outcome. *Br J Psychiatry* 169:371–378, 1996.
- Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC: Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*. 64:543–52, 2007.
- Meyer SE, Carlson GA, Wiggs EA, Martinez PE, Ronsaville DS, Klimes-Dougan B, Gold PW, Radke-Yarrow M: A prospective study of the association among impaired executive functioning, childhood attentional problems, and the development of bipolar disorder. *Dev Psychopathol* 16:461–476, 2004.
- Meyer SE, Carlson GA, Wiggs EA, Ronsaville DS, Martinez PE, Klimes-Dougan B, Gold PW, Radke-Yarrow M: A prospective high-risk study of the association among maternal negativity, apparent frontal lobe dysfunction, and the development of bipolar disorder. *Dev Psychopathol* 18:573–589, 2006.
- Meyer SE, Carlson GA, Youngstrom E, Ronsaville DS, Martinez PE, Gold PW, Hakak R, Radke-Yarrow M: Long-term outcomes of youth who manifested the CBCL-pediatric bipolar disorder phenotype during childhood and/or adolescence. *J Affect Disord* (epub before print July 15, 2008).
- Mick E, Spencer T, Wozniak J, Biederman J: Heterogeneity of irritability in attention-deficit/hyperactivity disorder subjects with and without mood disorders. *Biol Psychiatry* 58:576–582, 2005.
- Miklowitz DJ: Adjunctive psychotherapy for bipolar disorder: State of the evidence. *Am J Psychiatry*. 165:1408–1419, 2008.
- Moffitt TE, Caspi A, Rutter M: Strategy for investigating interactions between measured genes and measured environments. *Arch Gen Psychiatry* 62:473–481, 2005.
- Moore CM, Biederman J, Wozniak J, Mick E, Aleardi M, Wardrop M, Dougherty M, Harpold T, Hammerness P, Randall E, Lyoo IK, Renshaw PF: Mania, glutamate/glutamine and risperidone in pediatric bipolar disorder: A proton magnetic resonance spectroscopy study of the anterior cingulate cortex. *J Affect Disord* 99:19–25, 2007.
- O'Connor MJ, Shah B, Whaley S, Cronin P, Gunderson B, Graham J: Psychiatric illness in a clinical sample of children with prenatal alcohol exposure. *Am J Drug Alcohol Abuse* 28:743–754, 2002.
- Pavuluri MN, Graczyk PA, Henry DB, Carbray JA, Heidenreich J, Miklowitz DJ: Child- and family-focused cognitive behavioral therapy for pediatric bipolar disorder: Development and preliminary results. *J Am Acad Child Adolesc Psychiatry* 43:528–537, 2004.
- Pavuluri MN, Birmaher B, Naylor MW: Pediatric bipolar disorder: A review of the past 10 years. *J Am Acad Child Adolesc Psychiatry* 44:846–871, 2005.

- Pavuluri MN, Henry DB, Nadimpalli SS, O'Connor MM, Sweeney JA: Biological risk factors in pediatric bipolar disorder. *Biol Psychiatry* 60:936–941, 2006.
- Pavuluri MN, O'Connor MM, Harral E, Sweeney JA: Affective neural circuitry during facial emotion processing in pediatric bipolar disorder. *Biol Psychiatry* 62:158–167, 2007.
- Prendergast M, Taylor E, Rapoport JL, Bartko J, Donnelly M, Zametkin A, Ahearn MB, Dunn G, Wieselberg HM: The diagnosis of childhood hyperactivity. A U.S.-U.K. cross-national study of DSM-III and ICD-9. *J Child Psychol Psychiatry* 29:289–300, 1988.
- Rende R, Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Keller M: Childhood-onset bipolar disorder: Evidence for increased familial loading of psychiatric illness. *J Am Acad Child Adolesc Psychiatry* 46:197–204, 2007.
- Rich BA, Vinton DT, Roberson-Nay R, Hommer RE, Berghorst LH, McClure EB, Fromm SJ, Pine DS, Leibenluft E: Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. *Proc Natl Acad Sci USA* 103:8900–8905, 2006.
- Rich BA, Schmajuk M, Perez-Edgar KE, Fox NA, Pine DS, Leibenluft E: Different psychophysiological and behavioral responses elicited by frustration in pediatric bipolar disorder and severe mood dysregulation. *Am J Psychiatry* 2007 164:309–317, 2007.
- Ruggero CJ, Carlson GA, Kotov R, Bromet EJ: Long-term diagnostic consistency of bipolar disorder. American Psychopathological Association Annual Meeting, New York, NY, March 5–7, 2009.
- Rutter M, Kim-Cohen J, Maughan B: Continuities and discontinuities in psychopathology between childhood and adult life. *J Child Psychol Psychiatry* 47:276–295, 2006.
- Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, Lavori P, Lebowitz B, Rudorfer M, Frank E, Nierenberg AA, Fava M, Bowden C, Ketter T, Marangell L, Calabrese J, Kupfer D, Rosenbaum JF: Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry* 53:1028–1042, 2003.
- Schwartz JE, Fennig S, Tanenberg-Karant M, Carlson G, Craig T, Galambos N, Lavelle J, Bromet EJ: Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. *Arch Gen Psychiatry* 57:593–600, 2000.
- Shaw DS, Owens EB, Giovannelli J, Winslow EB: Infant and toddler pathways leading to early externalizing disorders. *J Am Acad Child Adolesc Psychiatry* 40:36–42, 2001.
- Speltz ML, DeKlyen M, Greenberg MT: Attachment in boys with early onset conduct problems. *Dev Psychopathol* 11:269–285, 1999.
- Thapar A, Rice F: Twin studies in pediatric depression. *Child Adolesc Psychiatr Clin N Am* 15:869–881, 2006.
- Tillman R, Geller B, Nickelsburg MJ, Bolhofner K, Craney JL, DelBello MP, Wigh W: Life events in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. *J Child Adolesc Psychopharmacol* 13:243–251, 2003.
- Volk HE, Todd RD: Does the Child Behavior Checklist Juvenile Bipolar Disorder Phenotype identify bipolar disorder? *Biol Psychiatry* 62:115–120, 2007.
- Youngstrom E, Meyers O, Youngstrom JK, Calabrese JR, Findling RL: Diagnostic and measurement issues in the assessment of pediatric bipolar disorder: Implications for understanding mood disorder across the life cycle. *Dev Psychopathol* 18:989–1021, 2006.
- Zahn-Waxler C, Mayfield A, Radke-Yarrow M, McKnew DH, Cytryn L, Davenport YB: A follow-up investigation of offspring of parents with bipolar disorder. *Am J Psychiatry* 145:506–509, 1988.

Address reprint requests to:

Robert L. Findling, M.D.

University Hospitals Case Medical Center

Case Western Reserve University School of Medicine

10524 Euclid Avenue

Cleveland, OH 44106

E-mail: robert.findling@UHhospitals.org