The Health Care Crisis of Childhood-Onset Bipolar Illness: Some Recommendations for Its Amelioration

Robert M. Post, M.D., and Robert A. Kowatch, M.D.

Objective: To describe new data on the incidence and impact of childhood- and adolescent-onset bipolar illness and make recommendations to help accelerate the acquisition of knowledge in this area.

Data Sources: Two large, multicenter outpatient studies in adults with DSM-IV bipolar disorder—the Systematic Treatment Enhancement Program for Bipolar Disorder and the Bipolar Collaborative Network—were the primary sources of retrospective data on age at onset.

Study Selection: We focused on the 2 retrospective studies because they supplied more immediate data on age at onset and long-term prognosis than current prospective studies.

Data Synthesis: The 2 studies revealed that 15% to 28% of adults experienced an onset of their illness prior to age 13 years. Those with childhood versus adult onset had a more severe, complicated, and adverse course of bipolar illness, assessed retrospectively and confirmed prospectively during naturalistic treatment. The time lag from onset of first symptoms to first treatment was strongly inversely related to age at onset and averaged 16.8 ± 10 years in those with childhood onset. Recommendations include defining temporary consensus threshold criteria for each bipolar subtype and their prodromes; conducting studies using less onerous than traditional designs, including randomized open comparisons to acquire preliminary data in this age cohort; and forming clinical and academic treatment outcome networks to more quickly acquire treatment outcome data in this understudied population.

Conclusions: The data reveal a very substantial rate of childhood-onset bipolar illness, extraordinary delays in onset to first treatment, and a very adverse long-term outcome. Several approaches to accelerating the rate of acquisition of treatment outcome data in this cohort are outlined.

(J Clin Psychiatry 2006;67:115–125)

Received May 10, 2005; accepted Oct. 8, 2005. From the Biological Psychiatry Branch, National Institute of Mental Health (NIMH), National Institutes of Health (NIH), Bethesda, Md. (Dr. Post), and the Department of Psychiatry, Cincinnati Children's Hospital Medical Center/University of Cincinnati Medical Center, Cincinnati, Ohio (Dr. Kowatch).

This research was supported (in part) by the Intramural Research Program of the NIMH, NIH.

Dr. Kowatch has served as a consultant to Eli Lilly, GlaxoSmithKline, Janssen, Otsuka, and Cephalon and has served on the speakers or advisory boards of AstraZeneca and Abbott. Dr. Post reports no additional financial or other relationships relevant to the subject of this article.

The views expressed here are solely the personal opinions of the authors and may not reflect the official positions of the NIMH, NIH, the federal government, or any other organization.

Corresponding author and reprints: Robert M. Post, M.D., Chief, Biological Psychiatry Branch, NIMH, NIH, Bldg. 10, Room 3S329, 10 Center Dr. MSC-1272, Bethesda, MD 20892-1272 (e-mail: robert.post@nih.gov).

Continuing controversies about the diagnostic boundaries of childhood-onset bipolar illness are worsening what had already been a deficit in treatment research and, as a consequence, health care. These boundary controversies[1–9] have created uncertainty about the ages at onset of the syndrome, the incidence and prevalence of childhood-onset bipolar disorder in the general population, and, most troubling, its appropriate treatment. These controversies also hamper the further development of treatment-related research in a field that desperately needs immediate information promulgated to parents and treating physicians.[10,11] The recently published treatment guidelines for children and adolescents with bipolar disorder by Kowatch et al.[11] are a good first step, but are confounded by a lack of systematic information about many widely used options, as well as strong ongoing academic dissent about the diagnostic boundaries of each subtype, but particularly bipolar II and bipolar not otherwise specified (NOS).[6,7]

Here we offer several perspectives on the magnitude of the problem and a series of potential approaches that could begin to close the information and treatment gaps at a more rapid pace than might otherwise occur with conventional academic grant–seeking approaches. The field is in agreement that prospective assessment and follow-up of large cohorts of children need to be conducted in order to better define initial diagnostic subgroups and their ultimate trajectories into classic bipolar illness presentations or other diagnoses.[7,11] With conventional clinically

derived populations, this process could take a decade, and, even using cohorts at high risk, many years would elapse before the results could produce more definitive information on diagnosis and naturalistic course of illness.

This delay will translate into millions of children in the United States alone receiving a wide range of diagnoses and therapeutic approaches, where there is little consensus about either beyond their application in children with clear bipolar I illness. The delay in both diagnosis and institution of appropriate treatment will not only lead to much suffering, but, to the extent that children with bipolar disorder and comorbid attention-deficit/hyperactivity disorder (ADHD) are mistakenly first being treated with stimulants or antidepressants without the protection of a mood stabilizer, could also produce harmful effects and exacerbate symptomatology, although the evidence for this possibility is not very systematic.[12–16] This issue is also obscured by the new controlled data that stimulants, when used as augmentation of a mood stabilizer, do not exacerbate mood.[17] Not addressed in a controlled fashion are the potential adverse effects of stimulant or antidepressant monotherapy in children with a bipolar syndrome.

THE EXTENT OF CHILDHOOD-ONSET BIPOLAR ILLNESS DERIVED FROM WELL-DIAGNOSED ADULTS: CONVERGENCE OF EPIDEMIOLOGIC DATA

How does one begin to circumvent these difficult impasses and the scientific challenges that drive them? One approach is to use information from well-diagnosed adults with bipolar illness and retrospectively examine their ages at onset and courses of treatment. This has been done in 2 relatively large cohorts derived from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[18] and the Bipolar Collaborative Network (BCN; formerly called the Stanley Foundation Bipolar Network, before funding was terminated in 2002).[19,20] The results are highly consistent both internally and with recent epidemiologic data.[21,22]

In the BCN,[19,20] 50% of the adults, with an average age of 42 years at Network entry, had illness onset prior to age 19 years, i.e., episodes that would meet current DSM-IV diagnostic criteria. Fifteen percent of the entire adult cohort of 521 patients had onset of bipolar illness prior to age 13 years. In the STEP-BD series of 913 DSM-IV–diagnosed patients, these figures were even higher—66% for illness onset prior to age 19 years and 28% prior to age 13 years.[18]

These data indicate that even 25 to 30 years ago there was a considerable prevalence of bipolar illness in very young children, i.e., in the group with onset before age 13 years. Why was this early onset previously not recognized, or the enormity of the problem of adolescent-onset bipolar illness? One explanation is that, in the BCN, the group with *childhood onset* (prior to age 13 years) had an average lag or delay from the onset of the first episode to the onset of first treatment for mania or depression of 16.8 ± 10 years.[19,20,23] The group with onset from ages 13 to 18 years (that we call *adolescent onset*) had a delay of first treatment of 11.3 ± 10 years. This lag decreased to an average of 4.6 ± 7 years in the early adult-onset group (aged 19–29 years), and, in the later adult-onset group (aged 30+ years), the lag was only 2.5 ± 5 years on average. Thus, it would appear that an egregiously large number of the children with manic and depressive symptoms associated with moderate-to-severe dysfunction were neither diagnosed nor treated for 10 to 15 years. This delay very likely had extremely adverse consequences, as noted in the next section.

If one takes the BCN figure of 15% of bipolar patients with early onset (prior to 13 years of age)[19,20] and assumes that the bipolar type I diagnosis represents about 1% of the U.S. population, this would yield about 420,000 children with the illness (without accounting for cohort or anticipation effects). If one uses the STEP-BD figure of 28% having onset prior to age 13 years[18] and assumes that the real incidence of bipolar illness (including bipolar II and bipolar NOS) is about 3%,[24–26] then this would yield an estimated prevalence of bipolar illness in children under age 13 in the United States of about 2,072,000.

The retrospective data from these 2 large adult cohorts parallel recent epidemiologic data of Kessler et al.[21,22] indicating that half of all lifetime mental illnesses begin by age 14. Similarly, in Kessler and colleagues' data,[21,22] delays to first treatment averaged 6 years for adults with mood disorders, and this lag increased in those with earlier ages at onset.

Another avenue to childhood-onset bipolar disorder is from those with prepubertal-onset dysthymic and major depressive disorders. Twenty percent to 40% of these children may become hypomanic or manic when treated with antidepressants and eventually have a bipolar disorder diagnosis.[27,28] Moreover, children of 2 parents with affective disorder (at least one being bipolar) are at a 70% lifetime risk of a unipolar or bipolar affective disorder.[29] As seen in adolescents,[30] early appropriate psychotherapeutic or pharmacologic intervention may help prevent the progression from a unipolar depressive to bipolar presentation. The risk of a switch into mania with antidepressants is directly related to an earlier age at onset of the depression.[31] This risk of conversion to a bipolar course is a continuing lifetime risk associated with each depressive recurrence and is estimated to be about 1% per year.[32]

THE POOR PROGNOSIS OF EARLY-ONSET BIPOLAR ILLNESS COMPARED WITH ADULT-ONSET ILLNESS

Both the BCN and STEP-BD findings are highly convergent in showing that those patients with childhood- or

adolescent-onset bipolar illness have increased morbidity and comorbidity and poor retrospective and prospective illness outcomes compared with those with adult onset.[18–20] Those with early onset were at a significantly higher risk ($p < .001$) for increased numbers of episodes and suicide attempts, increased incidence of anxiety disorder comorbidities, and, very problematically, an increased incidence of both alcoholism and drug abuse compared with those with adult onset.

In the BCN, where 513 patients were also prospectively daily assessed on the National Institute of Mental Health-Life Chart Method (NIMH-LCM) by clinicians, a variety of prospective measures confirmed a more adverse course of prospective illness. For example, those with early onset of bipolar disorder had an increased amount of time manic, time depressed, average severity of depression, and days of ultradian cycling and a decreased number of days euthymic despite naturalistic treatment.[19,20,23] Since these adults were treated prospectively by experts in the psychopharmacology of bipolar illness, these data indicate that those with childhood- or adolescent-onset illness are, in general, more treatment refractory as adults than those with early or late adult onset.

Although there may be some ambiguity about the primacy of a diagnosis of bipolar illness versus one of substance abuse in adolescents, it is highly likely that the substance abuse disorder diagnosis occurred after bipolar onset in the group with childhood onset (prior to age 13 years). The high rate of substance abuse comorbidity in early-onset bipolar illness[19,20] is consistent with Wilens and coauthors' findings[33,34] that adolescent-onset bipolar illness is associated with a much greater risk of substance abuse than that in prepubertal-onset children or adolescents in the general population.

The retrospective data for adults with childhood onset[18,20,23] also converge with the prospective data of Geller et al.[35] and others,[36] indicating that, after 2 and 4 years of follow-up, patients with childhood-onset bipolar illness had a poor outcome when treated naturalistically in the community. Moreover, in the study of Findling et al.[37] of children aged 5 to 17 years with bipolar disorder, relapse into a new mood episode on either lithium or divalproex monotherapy was not only very high (63.3%), but was also associated with an earlier age at onset of bipolar disorder. Dropouts from the study for any reason totaled 83.3%,[37] again indicating that very few of these patients do well long term on these conventionally accepted treatment modalities.[11]

Thus, when the adults in the BCN and STEP-BD series were children with unrecognized and untreated early-onset bipolar disorder, they and their families were most likely experiencing the considerable social and educational difficulties of not only their bipolar illness, but also an increased incidence of another set of alcohol and substance abuse comorbidities,[19,20,23,38,39] each of which presents as a difficult-to-treat entity in itself. Moreover, the presence of these comorbidities could further adversely affect or exacerbate the underlying neurobiological dysfunctions associated with bipolar illness itself.[40,41] Long delays in diagnosis and treatment may also contribute to the high prevalence of bipolar illness in those incarcerated in our prison system.[42]

Taken together, these observations help answer affirmatively the question left unresolved in the epidemiologic data of Wang et al.[21(p610)] as to whether the delays "to make initial treatment contacts truly pose a public health problem." The alternative possibility had been entertained and endorsed by others[43] that they may reflect "less severe, short-lived, or non-debilitating mental disorders."[21(p610)] The retrospective data noted here make it clear that the opposite perspective is correct, and those with the earliest onset of bipolar disorder (at least in the subgroup that does go to academic outpatient treatment and research settings) are most severely and adversely affected by the early onset and likely also by the extraordinarily long delays to first treatment.

THE DIAGNOSIS AND TREATMENT GAPS FOR CHILDHOOD-ONSET BIPOLAR ILLNESS: RECOMMENDATIONS TO ACCELERATE SOLUTIONS

There is, therefore, a substantial incidence rate of childhood-onset bipolar illness, revealed both in the retrospective studies described here (15%–28% of all bipolar disorder onset occurring prior to age 13)[18–20] and in prospective follow-up.[35,36] We suggest that the academic community begin to more rapidly forge some consensus and develop a series of operational measures based on the available evidence (Table 1). Such recommendations might include:

A. Reaching initial agreement about some of the fundamental aspects of childhood-onset bipolar illness.

This might involve:

(1) Ending the argument as to whether the bipolar-like syndrome exists in very young children in the affirmative.

Based on the retrospective and epidemiologic data noted above and a variety of other data in more directly assessed childhood cohorts, the first approach would be to cease arguments about the existence of the bipolar-like syndrome itself in children. Since childhood onset of bipolar disorder was recognized in the work of Kraepelin[44] and others more than a century ago, and the current data from many different sources are convergent and overwhelming, this issue could readily be resolved in the affirmative.

(2) Agreeing that bipolar illness affects a substantial number of children and the incidence may be increasing.

There are large numbers of children with bipolar disorder in the community and in clinical treatment set-

Table 1. The Diagnosis and Treatment Gaps in Childhood-Onset Bipolar Illness: Recommendations to Accelerate Solutions

A. Reach agreement about fundamental aspects of childhood-onset bipolar illness, i.e., that
   (1) A bipolar-like syndrome exists in very young children
   (2) This syndrome affects many children, and the incidence may be increasing
   (3) Despite differences about diagnostic thresholds, many of these children are severely ill and highly dysfunctional
   (4) All children with bipolar-like presentations may not proceed to the full syndrome in adolescence or adulthood

B. Set temporary, operationally defined thresholds on a continuum for defining a prodrome and full diagnosis for each bipolar subtype. This consensus process would
   (1) Allow revision of these illness thresholds when enough prospective follow-up data become available in the future
   (2) Allow better assessment of acute treatment responses and the prevention of illness recurrence or progression
   (3) Facilitate research grant acquisition
   (4) Address the high variability in cycle frequency inherent in bipolar illness
   (5) Recognize that symptoms may both progress and evolve with age as well as with duration of illness
   (6) Emphasize that prepubertal- and adolescent-onset forms of bipolar illness may greatly differ

C. Include heterogeneous illness presentations in treatment studies.

D. Encourage more practical clinical trials to assess comparative drug effectiveness and tolerability:
   (1) Foster randomized, open comparative studies
   (2) Encourage continuation phases for responders and crossovers or rerandomization for nonresponders
   (3) Encourage greater attention to the acquisition of treatment effectiveness data in the context of naturalistic outcome studies
   (4) Allow comparative strategies to be performed in an open fashion to achieve clinically useful information
   (5) Attempt to more systematically and qualitatively capture clinical practice experience
   (6) Begin to assess the sequencing and relative effectiveness of complex treatment regimens that are widely being used in clinical practice
   (7) Begin to assess clinical and biological markers of response to a given treatment or combination so that treatments can be better matched to individual patients

tings.[18–24] Whatever the incidence rate was 30 years ago, it is likely to be higher now because there is considerable evidence for both a cohort (year of birth) effect[45–47] and an anticipation (generational) effect conveying both an increased current number of children with the illness and an approximately 10-year earlier onset of their illness than their parents.[48] The combined cohort and anticipation effects are very likely why family members, advocacy groups,[49,50] private psychiatrists, treating clinics, and research groups are all troubled by the apparent increased appearance of children with bipolar-like symptoms, when they had previously seen much less of these disorders. It is also possible that increased awareness and changes in classification standards contribute as well, although these were not thought to be major factors in the careful review of Lange and McInnis.[48]

Accompanying these cohort and anticipation effects on age at onset and incidence may also be a concomitant increase in severity of the symptomatology,[48] such as that which occurs in very early (childhood) onset Huntington's chorea, for example. This potential increased severity might occur whether there are genetic or environmental mechanisms (or both) for the observed cohort and anticipation effects.

(3) Acknowledging the consensus view that, despite persisting differences about diagnostic thresholds, many of these children with bipolar-like presentations are severely ill and highly dysfunctional.

There is already wide agreement among families, school officials, clinicians, and treating physicians that children with bipolar-like syndromes can be severely affected and highly dysfunctional.[6,7,11] Despite the general lack of controversy about this point, it is nonetheless important to emphasize, because it increases the urgency to rapidly gain diagnostic clarity and initiate effective interventions.

(4) Acknowledging that all children with bipolar-like presentations may not proceed to the full syndrome in adolescence or adulthood.

Clinicians might focus on longitudinal assessment and encourage parents of children with likely bipolar disorder syndromes to participate in this process. Parents could rate their children on a daily prospective basis, either using the Kiddie-LCM or using the adult NIMH-LCM form (if their child is old enough and the manic and depressive symptoms are more clear), or some other equivalent systematic longitudinal assessment tool.[51–55] Given the heterogeneity of the illness and the changing course as a function of age and stage of illness, such a daily rating of symptom severity would be useful in clarifying the illness course and longitudinal trajectory, and in making careful assessments of the efficacy of therapeutic interventions. If the child was in an early moderately to severely symptomatic range, such a record might help parents to begin to both initiate and evaluate psychotherapeutic and psychopharmacologic interventions. This type of record would also facilitate clinical consultation should this be necessary in the future.

B. Set temporary, operationally defined thresholds on a continuum for defining the full diagnostic bipolar disorders and their potential prodromes.

The diagnosis of bipolar disorder could be operationally defined on a continuum, where for each syndrome meeting full DSM-IV criteria for bipolar I, II, or NOS illness, arbitrary thresholds are defined for possible bipolar prodrome, likely bipolar prodrome, likely full syndrome, and definite bipolar disorder meeting all DSM-IV criteria. Many medical illnesses develop on such a continuum in which the precise thresholds for disease onset are unclear and thresholds for treatment change over time, e.g., in hypertension, Parkinson's disease, and AIDS.

(1) Once the operational and symptom thresholds for the different levels of the prodrome and full syndrome are

designated by a consensus process, they can later be altered and refined, based on the empirical prospective data, in a more systematic and rational basis.

The same types of detailed revisions could not be achieved as readily if such agreed-upon information on thresholds is not collected from the outset. Such temporary criteria could readily be set in a consensus conference similar to that achieved by Kowatch and colleagues[11] in their consensus guidelines for the treatment of children with bipolar I illness. Bipolar II and bipolar NOS were not included in this guideline because few systematic treatment data exist for these subtypes in children. Initial attempts by Birmaher et al.[36] to diagnose these subtypes have now been validated in prospective follow-up. Those with bipolar NOS took the longest time to achieve remission, and many converted to bipolar II and bipolar I subtypes.[36]

Use of agreed-upon thresholds on a diagnostic continuum will allow more adequate definition of the different trajectories that may be observed prospectively in different subgroups of patients with the minimal or full prodrome versus likely or definite diagnosis, particularly as these may vary markedly as a function of age at onset as well. Similarly, the timing and age at onset of the many full and subsyndromal comorbidities of childhood-onset bipolar-like syndromes[56] could be better followed if they were linked to well-defined bipolar subtype full syndromes or prodromes.

It should be emphasized that such a consensus process would not broaden the current diagnostic criteria for the full syndrome; it would just make the criteria more specific to children and more precise in the boundary definitions, so that wider agreement about the full syndrome diagnosis could be achieved than is currently available.

Moreover, one could specifically exclude those meeting only the prodrome definitions from drug studies and use these carefully defined boundaries to narrow drug study focus. Setting these operational criteria would not imply that children would be put at higher risk of exposure to drug treatment because of such definitions. On the contrary, clinicians and investigators could explore whether early psychosocial interventions could prevent the conversion of the prodrome to the full syndrome or other form of long-term adversity.[36,57]

In addition, such a provisional threshold diagnostic system would better:

(2) Allow assessment of acute treatment response and prevention of illness progression.

Most importantly, such categorizing by threshold would allow more rapid acquisition of both open and systematic randomized controlled trial (RCT) data on efficacy, effectiveness, and overall outcome. This and the following recommendations, largely referring to treatment with drugs, could also readily be employed for other treatment modalities, including different types of individual and family psychotherapeutic and psychoeducational interventions.

(3) Facilitate research grant acquisition.

With some agreement about the temporary diagnostic thresholds, the support of grants from many different funding sources could be accelerated because skepticism based on this controversial element would be less likely to influence the review process.

(4) Address the variability in cycle frequency of bipolar presentations.

The emphasis on establishing diagnostic thresholds on a continuum also emphasizes the longitudinal course of symptom trajectory in what we already know to be a highly pleomorphic and variable course in adults. Bipolar disorder in adults ranges from highly discrete episodes with long well intervals to more rapid and continuous cycling, as well as ultra-rapid and ultradian cycling, with various qualities and severities of presenting symptomatology and degrees of functional impairment.[58–60] There is no reason to expect those with childhood onset to be more homogenous or less complex or to have fewer comorbidities than adults.

(5) Recognize that symptoms progress and evolve with age and that, eventually, a longitudinal diagnostic evaluation may supersede a cross-sectional one, no matter how intensive and detailed the latter is.

The problem of heterogeneous presentations is likely even more significant in prepubertal-onset bipolar disorder, in which virtually every pertinent bipolar-like symptom, whether or not it differentiates those with prepubertal-onset bipolar disorder from those with ADHD, increases in both incidence and severity with age in clinical cohorts with diagnoses confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS).[61] For example, in one study,[61] the incidence and severity of decreased need for sleep (which highly differentiated prepubertal-onset bipolar disorder from ADHD) increased with age, whereas hyperactivity, inattentiveness, and impulsivity (which were virtually identical in prepubertal-onset bipolar disorder and ADHD) also increased in incidence and severity as a function of age in both groups of children. In this regard, use of a clinician- or parent-based longitudinal rating system (as noted in Section A4) may yield particularly valuable information.

(6) Recognize that prepubertal- and adolescent-onset forms of bipolar illness may also differ greatly.

Thus, the age of the child, as well as the age at illness onset, has to be critically considered in the symptomatic presentation of illness.[56] This is one of the reasons for the different clinical perspectives about the illness when children with prepubertal-onset bipolar disorder are studied at different ages and durations of illness. The confounds are even greater if these prepubertal children are mixed in with those with adolescent onset, who often have few

symptoms prior to the explosive onset of their bipolar disorder in early or late teenage years.[61] The range of comorbidities may also differ substantially in the prepubertal adolescent–onset populations.[56]

It is equally clear that the quality of the presenting symptoms can markedly differ as a function of both a child's age and duration of the illness. For example, hypersexuality is not likely to be among the presenting or prominent symptoms in a 2- to 4-year-old, whereas it might be more prevalent as part of the syndrome in latency and preteen years. This change in quality also remains true for some types of depressive and psychotic symptoms that are often seen later than those in the irritability/dyscontrol cluster.[61,62]

C. Include heterogeneous illness presentations in treatment studies.

Investigators of the psychopharmacology of childhood-onset bipolar illness should not make the same mistakes as those that have occurred in the adult field, where there is a fair amount of systematic efficacy data in bipolar I disorder, but little information about drug efficacy in bipolar II and bipolar NOS[63,64] or about any of the subtypes when they are accompanied by common comorbidities such as alcohol and substance abuse.[65] Given that a large number of children (especially the youngest) present with the bipolar II or bipolar NOS full syndromes, rather than bipolar I,[6,36,66,67] these syndromes should be included in clinical trials, particularly since there is little current convincing evidence to suggest differential drug responsivity among these diagnostic subgroups in either adults or children.

Similarly, those with and without many of the comorbid psychiatric conditions that accompany childhood-onset bipolar disorder[56] should be included as well, so that information about representative patients[68] is also obtained. This has been, and continues to be, a major deficit in the research and clinical knowledge base in adult bipolar illness,[64,65] since these more complicated patients are typically excluded from RCTs. Youngsters with substance abuse were also excluded from the study of Findling et al.,[37] rendering their finding of a poor outcome on monotherapy (in a good prognosis subgroup) even more problematic.

Comorbid disorders are very frequent among children and adolescents with bipolar disorder.[56] The most common comorbid diagnosis among children and adolescents with bipolar disorder is ADHD. Several studies[69,70] have found that ADHD is more common in prepubertal-onset bipolar disorder than in adolescent-onset bipolar disorder. The rate of comorbid ADHD in prepubertal children is approximately 60% to 90%, whereas in adolescents the rate is often lower (30%–40%).

Another disorder that is frequently comorbid in children with bipolar disorder is conduct disorder. Kovacs and Pollock[71] found a 69% rate of conduct disorder among 26 bipolar children and adolescents. More recent studies suggest a lower rate of conduct disorder comorbidity (25.8%), but a much higher rate of eventual oppositional defiant disorder (95.7%) in prepubertal-onset bipolar disorder compared with oppositional defiant disorder in children with ADHD (61.7%; $p < .001$); anxiety disorders were also highly present in both groups in this recent study (67.7% in prepubertal-onset bipolar disorder vs. 43.2% in ADHD).[56]

Moreover, adolescents with bipolar disorder are 4 to 5 times more likely to develop a substance use disorder than those without bipolar disorder.[33,34] Including children with and without comorbid conditions will allow not only the evaluation of potential treatments in typical patients, but also the assessment of drug effectiveness in both the primary and the comorbid conditions.

D. Encourage more practical clinical trials to assess comparative drug effectiveness and tolerability.

Agreement about temporary diagnostic subtypes should also help to improve the acceptance of more clinically informative designs than the traditional RCTs with an exclusive parallel, placebo group. Such practical clinical trials have recently been endorsed by March et al.[68] Encouraging a new series of more efficient, less burdensome study designs would help to:

(1) Foster randomized, open comparative studies.

Partially controlled clinical trials could be used as a rapid source of new information that would greatly assist clinicians and patients. For example, if groups of practitioners or investigators were moving many of their patients from first-generation atypical antipsychotics (with their range of problems for weight gain) to the more recently approved and more weight-neutral atypicals (i.e., ziprasidone and aripiprazole), enormous benefit would be derived from a randomized assignment study of the 2 newer drugs. Evidence of tolerability and general effectiveness would be acquired even in the absence of significant differences in efficacy. The importance of systematic long-term assessment of tolerability in its own right in this developmentally vulnerable population cannot be overestimated, especially when drugs with demonstrated efficacy in adults are already being widely used alone and in combination in very young children[72] in the absence of systematic controlled data.

However, should efficacy differences emerge, one would have derived considerable benefit without a placebo-controlled arm. Such a randomized, comparative clinical trial could be performed in an unblind fashion to further facilitate ease of recruitment and completion of the study, because biases from a lack of blindedness are highly unlikely in the absence of any preliminary effectiveness data.[11,68,73] These same biases are also highly unlikely to affect the evaluation of important side effects

such as sedation, weight gain, paradoxical activation, vomiting, or akathisia.

Such an RCT of 2 "active" comparators is also the type of design parents most support, particularly in the very youngest children.[74] The cost and difficulty of completing an open randomized trial are remarkably reduced compared with a double-blind trial, and when long-term safety in the developing child is a critical issue, feasibility may be more important than degree of control.[68] For example, such a randomized, unmasked, practical, multicenter clinical trial produced highly informative and greatly needed clinical data to help drive physician and patient decision making about instituting immediate versus deferred antiepileptic drug treatment after a first seizure.[73]

(2) Encourage continuation phases for responders and crossovers or rerandomization for nonresponders.

Some clinical trials could be designed to allow and encourage continuation phases for responders and crossover of nonresponders to the other drug because these designs provide data critical to clinical decision making.[68,75,76] The purity of the double-blind, placebo-controlled, parallel group, short-term studies, with neither a continuation nor crossover phase included in the study (i.e., the traditional gold-standard RCT), does not provide patients, families, and clinicians with the much needed clinical information about the nature, quality, and duration of drug responsiveness nor develop data about the chances of response to the other, or another, drug.[68,75,76]

Instead, clinician friendly randomized designs (that do not rule out continuation and crossover phases) should be considered as viable alternatives,[68,74–79] in particular when safety concerns and allowance for early withdrawal for untoward side effects are needed.[76–78,80] Such a randomized, open, comparative clinical trial can readily be done in single sites or academic and clinician-based networks. Design and statistical approaches to rerandomized trials are discussed in detail by Boyle and Jadad[81] and Davis et al.[82]

(3) Encourage some systematization of treatment effectiveness data in "naturalistic" outcome studies.

Comparative outcome assessment could be added to the ongoing long-term "naturalistic" observational outcome studies of childhood-onset bipolar illness and its imitators. The status of naturalistic outcome studies in adults (for whom much is known about the general efficacy of a large group of agents[63]) is very different from that in children and adolescents, for whom there are very few systematic data available.

Long-term observational studies could:

(a) Randomize between 2 active options; knowledge could be rapidly advanced by randomizing between 2 drugs at every naturalistic therapeutic choice point that a clinician or investigator would make based on clinical need. For example, if use of a mood-stabilizing anticonvulsant were being considered, one could randomize between topiramate or valproate, valproate or carbamazepine, carbamazepine or oxcarbazepine, or any of these individual drugs randomized against lithium.[79]

(b) Randomize when augmentation is necessary; similarly, when augmentation agents are needed for any of the above regimens in order to treat breakthrough depression, one could randomize between 2 antidepressants with different mechanisms of action, between 2 different atypical antipsychotics with different tolerability profiles, or between an atypical antipsychotic versus an antidepressant or another mood stabilizer.

(c) Compare dose increases of the first agent versus adding a second agent; the randomization could even be between a dose increase of the first agent versus adding a second agent. Not only would such data from a randomized comparative assessment be invaluable to the practitioner in childhood bipolar disorder, but it would also provide the type of systematic data that are still lacking in the adult psychopharmacology of bipolar illness despite more than 30 years of traditional RCTs.

(4) Allow comparative strategies to be performed in an open fashion to achieve clinically useful information.

An adaptive treatment trial—i.e., one with a placebo-free design comparing a standard treatment, an innovative one, and the standard with a switch to the innovative agent at a preset threshold—could even be used for regulatory approval purposes if powered accordingly.[75] Smaller, even underpowered, studies would also be helpful if effect sizes were large or if the differences in side-effect burden were clinically meaningful.

(5) Attempt to capture clinical practice experience.

Agreement about temporary diagnostic thresholds would also facilitate the possible formation of a clinical trials network among practitioners, as recommended by the Adolescent Mental Health Initiative[83] and the NIMH Multidisciplinary Workgroup.[84] In this fashion, some of the vast clinical experience with drug responsivity in large numbers of children could be codified and captured in an open, uncontrolled fashion and help in the preliminary assessment of safety and tolerability, as well as the eventual design of more formal RCTs.

In a formal[85] or an informal clinical trials network, or in routine clinical practice, one could even achieve some clinically useful information from the most minimalistic of outcome measures, such as a single Clinical Global Impressions scale for Bipolar Illness (CGI-BP) rating[86] at the end of each acute and continuation intervention. This CGI-BP rating, along with endpoint dose, duration of treatment, and a tolerability statement, including whether any early exit was attributable to either lack of efficacy or to side effects, would provide very useful "first-look" information about outcomes in the relatively large number of children already exposed to such agents.

(6) Begin to assess complex treatment regimens.

Since many children with bipolar disorder are being treated with combination therapy,[11,72,87,88] and at times very complex combination therapy, use of daily prospective charting of mood, sleep, medications, and side effects would also facilitate the assessment of any given intervention, whether it be the addition, withdrawal, or substitution of a drug. Given the poor long-term outcomes[37,89] with monotherapy in children and adolescents with bipolar disorder, even in patients preselected for responsiveness to a given regimen,[37] one needs to begin to develop ways of comparing one complex regimen with another (as has been done in cancer chemotherapy clinical trials). The very high relapse rates in the 18-month randomized trial of lithium versus valproate monotherapy[37] further support the need for more systematic evaluation of combination therapies.

(7) Begin to assess clinical and biological markers of response to a given treatment or combination.

Clinical markers, or predictors of response, to a given agent could be built into each relative effectiveness trial. Neuroimaging studies could be closely linked to subsequent, even open treatment outcome trials to evaluate possible predictors of response.[90] And it would be invaluable if a small cluster of 15 to 30 candidate single nucleotide polymorphisms, previously studied in bipolar and other psychiatric illnesses, could be developed and made available for a range of clinical trials investigating prediction of treatment response. Such an approach is endorsed by Cox,[91] Hinds et al.,[92] and Newton-Cheh and Hirschhorn[93]; is relatively inexpensive and highly feasible[94]; and is likely to yield clinically important information about therapeutics in the very near future. Based on the assumption that children, like adults with bipolar illness, will have highly individualized degrees of responsivity to a given agent[80] or a given set of agents in combination, the early assessment of potential clinical and neurobiological markers of such individual responsivity to a given drug or combination would be of great clinical importance.

In addition, the same set of single nucleotide polymorphism profiles could simultaneously be used to evaluate potential vulnerability to illness onset or whether the illness progresses from a prodrome to full-blown syndrome in cohorts at high risk. Robust positive findings in this area would then help inform the risk-versus-benefit for drug treatment initiation. For example, if a child were in an early prodromal phase and the single nucleotide polymorphism profile suggested a very low risk for syndrome progression, one might follow with "watchful waiting," careful evaluation, and psychotherapeutic and psychosocial intervention. Conversely, in the face of early symptoms, high genetic and familial loading for bipolar illness, and a single nucleotide polymorphism profile suggesting considerable risk for progression to the full syndrome, early psychopharmacologic intervention might be more readily considered and initiated in a young child.

CONCLUSIONS

There is obviously a wide range of ways to facilitate the more rapid acquisition of treatment-related knowledge of bipolar and bipolar-like syndromes in children. In this article, we have presented a few of the many approaches that might help resolve the current crisis of conflicting opinion on most aspects of the diagnosis and treatment of childhood-onset bipolar disorder, except on the potential severity of symptomatology and adverse effects on the child, family, and community, for which there is little debate. Given the large number of children likely affected and the need for more immediate diagnostic clarity and therapeutic approaches that can be readily accepted by the psychiatric and general medical community, it would appear timely that several of these or related alternative perspectives be considered to better address this pressing problem.

Although much knowledge has recently been gained in the therapeutics of adult bipolar illness, the number of treatment-related grants or papers presented or published on bipolar illness remains much lower than in other major mental illnesses, such as schizophrenia.[63,79,95–97] Many of the fundamental questions about treatment of adult bipolar illness remain unanswered, such as, "What is the best approach to treatment of bipolar depression?"[63] The absence of definitive answers to this question in both adults and children is of great consequence, because several studies in naturalistically treated adult bipolar outpatients have found that time depressed exceeds time manic by a factor of 3,[59,60,98,99] and the age at onset of depression, time depressed, and number of depressive episodes correlate significantly with disability or cognitive deficits.[100,101]

At the same time, there is increasing recognition that a large subset of the adult bipolar patient population is moderately to highly treatment resistant and adversely affected by their illness in multiple domains of quality of life and functioning, despite the range of currently available treatments. As emphasized here, it is those patients with childhood and adolescent onset of their bipolar illness who are disproportionately represented in this poor prognosis group. The long-term implications of childhood-onset bipolar illness for morbidity, suicidality, and disability need to be carefully weighed against the potential benefits and adverse effects of the currently used mood stabilizers and atypical antipsychotics in assessing the risk-to-benefit ratio of any contemplated treatment.

Given the current recognition of the magnitude of the problem of childhood-onset bipolar illness and the stakes involved in its delayed or inadequate treatment, one can hope that a large range of different approaches will be considered by research clinicians. With the shortage of trained child psychiatrists in general, and those specializing in bipolar illness in particular, the lack of an agreed-upon body of evidence in the field will have an

even more telling effect. Parents, clinicians, psychiatrists, and other treating physicians (necessarily drawn from medical practices and specialties) are eager to acquire a more definitive core of knowledge about the most appropriate treatments for these highly ill children.[6,36,49,50]

The new guidelines of the Child Psychiatric Workgroup on Bipolar Disorder[11] are an example of an excellent first step toward expert consensus. However, as that work group acknowledged, neither of the 2 atypical antipsychotics (ziprasidone and aripiprazole) that may be better tolerated, nor the anticonvulsant oxcarbazepine, was even considered in the list of Stage 1 (monotherapy) to Stage 4 (combination) strategies in their suggested algorithms because of the "lack of any data regarding their use in children and adolescents with BPD."[11(p220)] Since long-term safety is a paramount consideration in childhood-onset bipolar illness, the exclusion of these and other potentially well-tolerated drugs from consideration represents a very major knowledge and practice gap.

In the Kowatch et al. guidelines,[11] only lithium provided highly rigorous (level A) evidence from a placebo-controlled RCT in children or adolescents. Of the 13 other agents discussed, all had evidence only at the lower levels B (i.e., RCT in adults), C (open trials in youngsters), or D (case reports or panel consensus). Thus, randomized comparative trials (on either an open or blind basis and possible extensions for responders and crossovers to the other agent for nonresponders) might more rapidly supply critical effectiveness and tolerability data to inform expert consensus and clinical practice. Acquisition of data in children at what might be considered an intermediate level of evidence, such as randomized, blind, comparative trials (perhaps labeled A-2) as in Findling et al.,[37] or randomized, open comparative trials (perhaps labeled A-3) as in Kowatch et al.,[102] is important in helping to inform clinical decision making. These and other less formal approaches[103–105] could be fostered while one awaits further data from the gold-standard, placebo-controlled RCT.[106,107]

Even if a series of preliminary guidelines is based on incomplete evidence and evolves as new information becomes available, it is vastly more desirable than remaining relatively data impoverished while waiting for definitive answers. Much clinically relevant knowledge can be drawn from other designs and approaches, some of which could be pursued more rapidly and systematically given the potentially enormous public health benefit.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), divalproex (Depakote), lithium (Lithobid, Eskalith, and others), oxcarbazepine (Trileptal), topiramate (Topamax), ziprasidone (Geodon).

REFERENCES

1. Carlson GA. Mania and ADHD: comorbidity or confusion. J Affect Disord 1998;51:177–187
2. Biederman J, Klein RG, Pine DS, et al. Resolved: mania is mistaken for ADHD in prepubertal children. J Am Acad Child Adolesc Psychiatry 1998;37:1091–1096
3. Biederman J, Faraone S, Wozniak J, et al. Further evidence of unique developmental phenotypic correlates of pediatric bipolar disorder: findings from a large sample of clinically referred preadolescent children assessed over the last 7 years. J Affect Disord 2004;82:S45–S58
4. Geller B, Williams M, Zimerman B, et al. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. J Affect Disord 1998;51:81–91
5. Leibenluft E, Charney DS, Towbin KE, et al. Defining clinical phenotypes of juvenile mania. Am J Psychiatry 2003;160:430–437
6. National Institute of Mental Health research roundtable on prepubertal bipolar disorder. J Am Acad Child Adolesc Psychiatry 2001;40:871–878
7. McClellan J. Commentary: treatment guidelines for child and adolescent bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005;44:236–239
8. Harris J. The increased diagnosis of "juvenile bipolar disorder": what are we treating? Psychiatr Serv 2005;56:529–531
9. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 2005;44:846–871
10. Faedda GL, Baldessarini RJ, Suppes T, et al. Pediatric-onset bipolar disorder: a neglected clinical and public health problem. Harv Rev Psychiatry 1995;3:171–195
11. Kowatch RA, Fristad M, Birmaher B, et al, and the Child Psychiatric Workgroup on Bipolar Disorder. Treatment guidelines for children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005;44:213–235
12. Biederman J, Mick E, Spencer TJ, et al. Therapeutic dilemmas in the pharmacotherapy of bipolar depression in the young. J Child Adolesc Psychopharmacol 2000;10:185–192
13. Post RM, Chang KD, Findling RL, et al. Prepubertal bipolar I disorder and bipolar disorder NOS are separable from ADHD. J Clin Psychiatry 2004;65:898–902
14. Wozniak J, Biederman J, Richards JA. Diagnostic and therapeutic dilemmas in the management of pediatric-onset bipolar disorder. J Clin Psychiatry 2001;62(suppl 14):10–15
15. DelBello MP, Soutullo CA, Hendricks W, et al. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. Bipolar Disord 2001;3:53–57
16. Craney JL, Geller B. A prepubertal and early adolescent bipolar disorder-I phenotype: review of phenomenology and longitudinal course. Bipolar Disord 2003;5:243–256
17. Scheffer RE, Kowatch RA, Carmody T, et al. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. Am J Psychiatry 2005;162:58–64
18. Perlis RH, Miyahara S, Marangell LB, et al. 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
19. Leverich GS, McElroy SL, Suppes T, et al. Early physical and sexual abuse associated with an adverse course of bipolar illness. Biol Psychiatry 2002;51:288–297
20. Leverich GS, Altshuler LL, Frye MA, et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. J Clin Psychiatry 2003;64:506–515
21. Wang PS, Berglund P, Olfson M, et al. Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:603–613
22. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593–602
23. Leverich GS, Post RM. Earlier age of onset and more severe course of bipolar illness in those with a history of childhood trauma: clinical and theoretical implications [commentary]. Lancet. In press
24. Hirschfeld RM, Calabrese JR, Weissman MM, et al. Screening for bipolar disorder in the community. J Clin Psychiatry 2003;64:53–59
25. Akiskal HS, Bourgeois ML, Angst J, et al. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. J Affect Disord 2000;59(suppl 1):S5–S30
26. Angst J, Gamma A, Benazzi F, et al. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003;73:133–146

27. Kovacs M, Akiskal HS, Gatsonis C, et al. Childhood-onset dysthymic disorder: clinical features and prospective naturalistic outcome. Arch Gen Psychiatry 1994;51:365–374
28. Geller B, Zimerman B, Williams M, et al. Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. Am J Psychiatry 2001;158:125–127
29. Lapalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. Can J Psychiatry 1997;42:623–631
30. Kochman FJ, Hantouche EG, Meynard JA, et al. A randomized trial of an interpersonal/cognitive behavior intervention for preventing bipolar disorder in depressed adolescents: preliminary results. Bipolar Disord 2003;5:62
31. Martin A, Young C, Leckman JF, et al. Age effects on antidepressant-induced manic conversion. Arch Pediatr Adolesc Med 2004;158:773–780
32. Angst J, Sellaro R, Stassen HH, et al. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. J Affect Disord 2005;84:149–157
33. Wilens TE, Biederman J, Forkner P, et al. Patterns of comorbidity and dysfunction in clinically referred preschool and school-age children with bipolar disorder. J Child Adolesc Psychopharmacol 2003;13:495–505
34. Wilens TE, Biederman J, Kwon A, et al. Risk of substance use disorders in adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2004;43:1380–1386
35. Geller B, Tillman R, Craney JL, et al. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch Gen Psychiatry 2004;61:459–467
36. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry. In press
37. Findling RL, McNamara NK, Youngstrom EA, et al. Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005; 44:409–417
38. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001;158:420–426
39. Frye MA, Altshuler LL, McElroy SL, et al. Gender differences in prevalence, risk, and clinical correlates of alcoholism comorbidity in bipolar disorder. Am J Psychiatry 2003;160:883–889
40. Post RM, Post SLW. Molecular and cellular developmental vulnerabilities to the onset of affective disorders in children and adolescents: some implications for therapeutics. In: Steiner H, ed. Handbook of Mental Health Interventions in Children and Adolescents. San Francisco, Calif: Jossey-Bass; 2004:140–192
41. Post RM, Speer AM, Hough CJ, et al. Neurobiology of bipolar illness: implications for future study and therapeutics. Ann Clin Psychiatry 2003;15:85–94
42. Elhaj O, Calabrese JR. The prevalence and phenomenology of bipolar disorder in Ottawa county jail, Ohio. Neuropsychopharmacology 2004;29:s99–s100
43. Narrow WE, Rae DS, Robins LN, et al. Revised prevalence estimates of mental disorders in the United States: using a clinical significance criterion to reconcile 2 surveys' estimates. Arch Gen Psychiatry 2002;59: 115–123
44. Kraepelin E. Manic-Depressive Insanity and Paranoia. Edinburgh, Scotland: ES Livingstone; 1921
45. Gershon ES, Hamovit JH, Guroff JJ, et al. Birth-cohort changes in manic and depressive disorders in relatives of bipolar and schizoaffective patients. Arch Gen Psychiatry 1987;44:314–319
46. Klerman GL, Weissman MM. Increasing rates of depression. JAMA 1989;261:2229–2235
47. Ryan ND, Williamson DE, Iyengar S, et al. A secular increase in child and adolescent onset affective disorder. J Am Acad Child Adolesc Psychiatry 1992;31:600–605
48. Lange KJ, McInnis MG. Studies of anticipation in bipolar affective disorder. CNS Spectr 2002;7:196–202
49. Coyle JT, Pine DS, Charney DS, et al. Depression and bipolar support alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in children and adolescents. J Am Acad Child Adolesc Psychiatry 2003;42:1494–1503
50. Hellander M. Pediatric bipolar disorder: the parent advocacy perspective. Biol Psychiatry 2003;53:935–937
51. Leverich GS, Post RM. Life charting the course of bipolar disorder. Curr Rev Mood Anxiety Disord 1996;1:48–61
52. Leverich GS, Post RM. Life charting of affective disorders. CNS Spectr 1998;3:21–37
53. Denicoff KD, Leverich GS, Nolen WA, et al. Validation of the prospective NIMH-Life-Chart Method (NIMH-LCM-p) for longitudinal assessment of bipolar illness. Psychol Med 2000;30:1391–1397
54. Denicoff KD, Ali SO, Sollinger AB, et al. Utility of the daily prospective National Institute of Mental Health Life-Chart Method (NIMH-LCM-p) ratings in clinical trials of bipolar disorder. Depress Anxiety 2002;15:1–9
55. Fristad MA, Arnold JSG. Raising a Moody Child: How to Cope With Depression and Bipolar Disorder. New York, NY: Guilford Press; 2004
56. Tillman R, Geller B, Bolhofner K, et al. Ages of onset and rates of syndromal and subsyndromal comorbid DSM-IV diagnoses in a prepubertal and early adolescent bipolar disorder phenotype. J Am Acad Child Adolesc Psychiatry 2003;42:1486–1493
57. Brent DA. The rewards of reducing risk [editorial]. Arch Pediatr Adolesc Med 2004;158:824–825
58. Post RM, Denicoff KD, Leverich GS, et al. Presentations of depression in bipolar illness. Clin Neurosci Res 2002;2:142–157
59. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH Life Chart Method. J Clin Psychiatry 2003;64:680–690
60. Nolen WA, Luckenbaugh DA, Altshuler LL, et al. Correlates of 1-year prospective outcome in bipolar disorder: results from the Stanley Foundation Bipolar Network. Am J Psychiatry 2004;161:1447–1454
61. Luckenbaugh DA, Findling RL, Leverich GS, et al. Earliest symptoms discriminating prepubertal onset bipolar illness from ADHD. Presented at the NIMH Pediatric Bipolar Conference; April 15–16, 2005; Coral Gables, Fla
62. Fergus EL, Miller RB, Luckenbaugh DA, et al. Is there progression from irritability/dyscontrol to major depressive and manic symptoms? a retrospective community survey of parents of bipolar children. J Affect Disord 2003;77:71–78
63. Keck PE Jr, Perlis RH, Otto MW, et al. The Expert Consensus Guideline Series: Treatment of Bipolar Disorder 2004. Postgrad Med Special Report 2004;December:1–120
64. Post RM, Speer AM, Obrocea GV, et al. Acute and prophylactic effects of anticonvulsants in bipolar depression. Clin Neurosci Res 2002;2: 228–251
65. Sonne SC, Brady KT. Substance abuse and bipolar comorbidity. Psychiatr Clin North Am 1999;22:609–627, ix
66. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. Bipolar Disord 2000;2:281–293
67. Tillman R, Geller B. Definitions of rapid, ultrarapid, and ultradian cycling and of episode duration in pediatric and adult bipolar disorders: a proposal to distinguish episodes from cycles. J Child Adolesc Psychopharmacol 2003;13:267–271
68. March JS, Silva SG, Compton S, et al. The case for practical clinical trials in psychiatry. Am J Psychiatry 2005;162:836–846
69. Faraone SV, Biederman J, Wozniak J, et al. Is comorbidity with ADHD a marker for juvenile-onset mania? J Am Acad Child Adolesc Psychiatry 1997;36:1046–1055
70. West SA, McElroy SL, Strakowski SM, et al. Attention deficit hyperactivity disorder in adolescent mania. Am J Psychiatry 1995;152:271–273
71. Kovacs M, Pollock M. Bipolar disorder and comorbid conduct disorder in childhood and adolescence. J Am Acad Child Adolesc Psychiatry 1995;34:715–723
72. Duffy FF, Narrow WE, Rae DS, et al. Concomitant pharmacotherapy among youths treated in routine psychiatric practice. J Child Adolesc Psychopharmacol 2005;15:12–25
73. Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet 2005;365:2007–2013
74. Post RM, Leverich GS, Fergus E, et al. Parental attitudes towards early intervention in children at high risk for affective disorders. J Affect Disord 2002;70:117–124
75. Dawson R, Lavori PW. Placebo-free designs for evaluating new mental health treatments: the use of adaptive treatment strategies. Stat Med 2004;23:3249–3262
76. Post RM, Luckenbaugh DA. Unique design issues in clinical trials of patients with bipolar affective disorder. J Psychiatr Res 2003;37:61–73

77. Rush AJ, Post RM, Nolen WA, et al. Methodological issues in developing new acute treatments for patients with bipolar illness. Biol Psychiatry 2000;48:615–624
78. Post RM, Denicoff KD, Leverich GS. Special issues in trial design and use of placebo in bipolar illness [commentary]. Biol Psychiatry 2000; 47:727–732
79. Post RM, Speer AM, Leverich GS. Bipolar illness: which critical treatment issues need studying? Clin Approaches in Bipolar Disord 2003; 2:24–30
80. Post RM, Keck JP, Rush AJ. New designs for studies of the prophylaxis of bipolar disorder. J Clin Psychopharmacol 2002;22:1–3
81. Boyle MH, Jadad AR. Lessons from large trials: the MTA study as a model for evaluating the treatment of childhood psychiatric disorder. Can J Psychiatry 1999;44:991–998
82. Davis SM, Koch GG, Davis CE, et al. Statistical approaches to effectiveness measurement and outcome-driven re-randomizations in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies. Schizophr Bull 2003;29:73–80
83. Evans DL, Beardslee W, Biederman J, et al. Depression and bipolar disorder. In: Evans DL, Foa EB, Gur RE, et al, eds. Treating and Preventing Adolescent Mental Health Disorders. New York, NY: Oxford University Press; 2005:3–27
84. Costello EJ, Pine DS, Hammen C, et al. Development and natural history of mood disorders. Biol Psychiatry 2002;52:529–542
85. Rendell JM, Juszczak E, Hainsworth J, et al. Developing the BALANCE trial: the role of the pilot study and start-up phase. Bipolar Disord 2004; 6:26–31
86. Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997;73:159–171
87. Kowatch RA, Sethuraman G, Hume JH, et al. Combination pharmacotherapy in children and adolescents with bipolar disorder. Biol Psychiatry 2003;53:978–984
88. Pavuluri MN, Henry DB, Devineni B, et al. A pharmacotherapy algorithm for stabilization and maintenance of pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry 2004;43:859–867
89. Kafantaris V, Coletti DJ, Dicker R, et al. Lithium treatment of acute mania in adolescents: a placebo-controlled discontinuation study. J Am Acad Child Adolesc Psychiatry 2004;43:984–993
90. DelBello MP, Cecil KM, Adler CM, et al. Neurochemical effects of olanzapine in first-hospitalization manic adolescents: a proton magnetic resonance spectroscopy study. Neuropsychopharmacol 2005 Nov 2 [Epub ahead of print]
91. Cox DR. Human genetic variation and common disease: a short-term approach for improving human health. NIH Director's Lecture; October 13, 2004; Bethesda, Md.
92. Hinds DA, Stuve LL, Nilsen GB, et al. Whole-genome patterns of common DNA variation in three human populations. Science 2005;307: 1072–1079
93. Newton-Cheh C, Hirschhorn JN. Genetic association studies of complex traits: design and analysis issues. Mutat Res 2005;573:54–69
94. Freeman B, Smith N, Curtis C, et al. DNA from buccal swabs recruited by mail: evaluation of storage effects on long-term stability and suitability for multiplex polymerase chain reaction genotyping. Behav Genet 2003;33:67–72
95. Goodwin GM. Bipolar disorder: is psychiatry's Cinderella starting to get out a little more? Acta Neuropsychiatr 2000;12:105
96. Baldessarini RJ. Treatment research in bipolar disorder: issues and recommendations. CNS Drugs 2002;16:721–729
97. Prien RF, Potter WZ. NIMH workshop report on treatment of bipolar disorder. Psychopharmacol Bull 1990;26:409–427
98. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
99. Kupka RW, Luckenbaugh DA, Post RM, et al. Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. Am J Psychiatry 2005;162:1273–1280
100. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? J Neurol Neurosurg Psychiatry 2004;75:1662–1666
101. MacQueen GM, Young LT, Robb JC, et al. Effect of number of episodes on wellbeing and functioning of patients with bipolar disorder. Acta Psychiatr Scand 2000;101:374–381
102. Kowatch RA, Suppes T, Carmody TJ, et al. Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2000;39: 713–720
103. DelBello MP, Kowatch RA, Warner J, et al. Adjunctive topiramate treatment for pediatric bipolar disorder: a retrospective chart review. J Child Adolesc Psychopharmacol 2002;12:323–330
104. Barzman DH, DelBello MP, Kowatch RA, et al. The effectiveness and tolerability of aripiprazole for pediatric bipolar disorders: a retrospective chart review. J Child Adolesc Psychopharmacol 2004;14: 593–600
105. Findling RL, McNamara NK, Gracious BL, et al. Combination lithium and divalproex sodium in pediatric bipolarity. J Am Acad Child Adolesc Psychiatry 2003;42:895–901
106. DelBello MP, Schwiers ML, Rosenberg HL, et al. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry 2002;41:1216–1223
107. Geller B, Cooper TB, Sun K, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc Psychiatry 1998;37: 171–178

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Melissa P. DelBello, M.D., at delbelmp@email.uc.edu.