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Pediatric Bipolar Disease: Current and Future Perspectives for Study of its Long-term Course and Treatment

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Abstract

Aim and Methods—Findings from recent long-term, prospective longitudinal studies of the course, outcome, and naturalistic treatment of adults with bipolar illness are highlighted as background for long-term developmental study of pediatric bipolar illness.

Results—Accumulating knowledge of bipolar illness in adults underscores a high risk for multiple recurrences through the lifespan, significant medical morbidity, high rates of self-harm, economic and social burden, and frequent treatment resistance with residual symptoms between major episodes. At present, there is no empirical foundation to support any assumption about the long-term course or outcome of bipolar illness when it arises in childhood or adolescence, or the effects of conventional pharmacotherapies in altering its course and limiting potentially adverse outcomes. The proposed research articulates specific descriptive aims that draw on adult findings, and outlines core methodological requirements for such an endeavor.

Conclusions—Innovations in the description and quantitative analysis of prospective longitudinal clinical data must now be extended to large, systematically ascertained pediatric cohorts recruited through multi-center studies if there is to be a meaningful scientific advance in our knowledge of the enduring effects of bipolar illness and the potential value of contemporary approaches to its management.

Keywords

bipolar illness; early-onset; pediatric; developmental; course; outcome

A new clinical wisdom has emerged concerning bipolar illness that emphasizes high risk of recurrence through the lifespan, complex genetic liability, economic and social burden, substantial risk of self harm, frequent resistance to pharmacotherapies, and persistence of residual symptoms between major episodes (1,2). These facts underscore the critical importance of early identification and have been impetus for bringing fresh attention to the pediatric age group with several expert panels recently summarizing clinical and methodological priorities for research in the area (3-4).

Evidence that pediatric affective disorders continue into adulthood (5-7), that neurocognitive abnormalities may persist after clinical remission (8), and that separate genes may differentially influence age of onset (9) are strong rationale for understanding how early onset bipolar illness impinges on long-term development. In the clinical domain, no validated treatment algorithm currently exists as the literature to date is comprised largely of anecdotal accounts, small case series, and few large scale open label studies employing objective measures of clinical response (10). This void has left both clinicians and parents with the paradox of managing an indisputably handicapping illness uncertain of the risk to children of medications whose long-term effects have been little studied. It is hardly surprising that treatments received by youth with bipolar illness are so variable and that lack of treatment is not uncommon (11). The real world clinical challenge is that absent long-term, large-scale multi-site naturalistic studies of pediatric cohorts, authoritative risk/benefit analyses are not even remotely feasible, leaving treatment decisions hanging on the vagaries of inference, hunch, and conjecture.

The purpose of this article is to outline a scientifically informed framework for the long-term observational study of pediatric bipolar illness that extrapolates data from prospective, naturalistic longitudinal research on adult bipolar disease. Because any assumption about the long-term implications of early bipolar illness remains unconfirmed, the adult literature is a necessary starting point for identifying critical benchmarks for prospective studies of illness course, outcome predictors, and treatment effects in children and youth. We therefore review selective aspects of this literature to highlight where the gaps in our knowledge lie, enumerate aims essential to advancing scientific knowledge of psychopathology, nosology, therapeutics and long-term repercussions on social adjustment, and outline necessary methodological prerequisites for such an endeavor.

It has been over eight decades since Kraepelin (12) documented the pleomorphic expression of bipolar illness in adults and how its long-term course shifted dynamically over time. Whether or not young people with bipolar illness show similar long-term variations in course, and whether or not long-term outcome can be reliably predicted, is unknown; to date, no prospective study has observed the course of pediatric patients as they transition to adolescence, and then to adulthood. As such, the questions are many:

- Do the major phenotypes that comprise bipolar illness (e.g., bipolar type I versus type II) remain stable over time in young patients, or does disease expression change as they mature. Does the chronic, irritable, phenotype that is believed to be prototypic of very young bipolars (13) persist across developmental stages, or do these patients eventually express course features seen commonly in adults such as monophasic episodes and lengthy well periods as they age?
- Is the long-term course more malignant, i.e., are recurrences more frequent, when the illness begins in childhood compared to adolescence, and do teens have greater propensity for lifetime recurrence than adults? Does a propensity for frequent recurrence in youth foreshadow chronicity in adulthood?
- Is progressive psychosocial deterioration characteristic of prepubertal bipolar illness? Does very early onset of disease predict increased liability for substance abuse and suicidality compared to when the illness onsets in adolescence?
- Are the variables that predict episode recovery and recurrence in preteens, teens, and adults identical, do course predictors remain stable over time, and are the effects of somatic therapy and psychotherapy in mediating outcome consistent across age groups?

These are but a fraction of the substantive questions that require attention in prospective, naturalistic, longitudinal research on early onset bipolar illness if it's unique and enduring vulnerabilities are to be fully understood.

Limited Data on the Nosological Validity_and Long-term Prospective Course of Pediatric Bipolar Illness

It is not merely that knowledge of pediatric bipolar illness is scant; there remains sharp controversy over its very diagnosis. As several authors note (14-16), systematically integrated efforts to establish its construct validity remain few in number, and these, especially studies conducted on preadolescent samples, have not gone unchallenged (17). Likewise, the pediatric literature has largely been silent in addressing the fundamental conceptual difference that exists between mania on the one hand and bipolar disorder on the other, a distinction especially problematic in child psychiatry given the overlap in symptoms complexes that comprise syndromes of mania, attention deficit disorder, and idiopathic organic states (16). Thus, we take up the issue of long-term observational research in the pediatric group with this caveat: the developmental continuity of preadolescent mania with adult bipolar affective disease remains undetermined (we will, however, use the term 'bipolar illness' throughout the text for convenience, mindful nonetheless of the controversy that remains). Establishing not simply the descriptive validity of mania in preadolescence, but its validity as a meaningful nosological taxon, remains a preeminent scientific concern. Although approaches needed to address this particular question is beyond the scope of the present article, the potential value of long-term observational studies of course and outcome in shedding new light on the issue will be briefly noted.

It suffices to say that data on the longitudinal course of pediatric bipolar disease are sparse. One (18) prospective study of five years duration has observed the course of bipolar illness in 54 adolescents starting from their index psychiatric hospital admission; a second (19) followed an outpatient cohort of 86 subjects as they approached their adolescence; a third (20) used a prospective design to follow the post-recovery course of 25 clinically ascertained subjects, 9- to 16-years of age, over 4- to 5-years; a fourth (21), using a catch-up longitudinal design, assessed time to recovery at one and four years after intake in a small sample of boys with comorbid ADHD; a fifth study (22-24) has reported on the continuity of bipolar syndromes, mainly BP-II and subacute illness, from adolescence to adulthood in a community ascertained sample of only 18 subject; and a sixth study (25) used a catch-up, follow-up design in reporting rates of recovery and relapse in a sample of 30 children and adolescents 4-5 years after their index episode. Thus, current knowledge of the prospective temporal patterns of episode recovery and recurrence in pediatric onset bipolar illness comes from but a handful of studies reporting on morbidity over relatively short periods of observation. Moreover, generalizability of these finding to the larger spectrum of pediatric bipolar disease is limited, as most of these studies (18-20;25) recruited only actively ill bipolar type I subjects with classic manic elation and/or grandiosity. While these cohorts have minimal diagnostic overlap with behaviorally severe forms of attention deficit disorder, the course of bipolar II illness, the still fuzzy BP-Not Otherwise Specified (NOS) phenotype, and bipolar syndromes associated with psychosis and substance use comorbidity remain unstudied. Moreover, while it is prudent on both clinical and methodological grounds to define the phenotype of mania in preadolescence as narrowly as possible until questions regarding its broader nosological validity are resolved (19), some (14-16) argue it is far from certain that the average young child or his/her parents can intuit the meaning of diagnostic questions tied to constructs such as 'elation' or 'euphoria', that clinicians in routine practice can reliably agree on their measurement, or that even experienced clinicians can agree on what differentiates manic excitement secondary to severe externalizing disorders from primary affective disease.

Also sparse are data on functional outcome associated with pediatric bipolar illness, with only two reports having described significant levels of psychosocial impairment and suicidality cross-sectionally in children (26) and teens (22-24). However, future efforts in this area will be complicated by the frequent diagnostic comorbidity of juvenile mania with externalizing disorders, a confounding muddled even further by the presence in these children of not one but *multiple* different diagnostic conditions. How to statistically parse the effects on functional outcome that arise singly from bipolar illness rather than from these associated psychiatric morbidities will require careful methodological attention. The importance of controlling for diagnostic comorbidity and for multimorbidity in studies of adaptive function in pediatric mania has been discussed by Carlson et al. (16,27,28).

Likewise, although open label (29-37) and several placebo controlled (38-40) studies of mood stabilizing agents in pediatric mania have been reported, neither long-term efficacy nor effectiveness data obtained on large samples presently exist. The value of maintenance pharmacotherapy has been reported in some studies (29,41), but not in others (20).

Deserving mention here is a rarely considered, though critically important, issue concerning the inherent unreliability of short-term observational data. Since most subjects recruited into longitudinal studies are symptomatic and treatment seeking at study entry, the severity and duration characteristics of the index episode are frequently anomalous compared to episodes observed later on. Subjects in the midst of such unusually long index episodes thus provide truncated information on recovery time and recurrence risks during an initial period of follow-up, potentially confounding estimates of cycle length early in the prospective course. Also, depending on how long the subject has been ill at study intake, retrospective dating of episode onset is less precise compared to the timing of new recoveries and recurrences that are observed prospectively. The degree to which such episode length and severity biases may distort estimates of early clinical course features of pediatric bipolar illness is inferred from data on the 18 teenage subjects with bipolar illness described by Lewinsohn et al. (22). Illness duration in this sample ranged from 0.7 to 125.0 months, with a median and mean of 48.3 and 50.4 months, respectively. Duration of the most recent episode ranged from 0.2 to 96.0 months, with a median and mean of 10.8 and 20.0 months, respectively. However, 11 of the 18 subjects were ill at the time of the index assessment and, not surprisingly, it was in this subgroup that the course was most chronic. Specifically, median duration of illness among currently ill subjects was 69.0 months compared to 13.2 months for subjects who were asymptomatic at the time of ascertainment. Similarly, the median duration of an episode was 39.7 months for currently ill subjects, compared with 13.1 months for the asymptomatic subjects. An added note of caution applies here in that all but 2 of these subjects met criteria not for mania but for BP II, there is insufficient description in the report of how episode onset and offset were determined, and the degree to which the temporal findings pertain to effects of hypomania, dysphoria, or the associated behavioral difficulties inherent to BP II illness remains uncertain. These qualifications aside, what we can surmise from these observations is that only by following samples through the multiple cycles of recovery and recurrence that accrue over extended time periods will it be possible to depict the course of pediatric bipolar illness and identify prognostic variables and treatment effects unconfounded by biases inherent in short-term follow-up observations. The clinical implications of such extended observational study for reliably informed treatment related decisions are self-evident.

Does maturation affect temporal aspects of episode recovery, recurrence, subsyndromal symptoms, chronicity, suicidality, and length of well-intervals? Only limited data exist but there is at least a tentative suggestion that this may be so. Manic children studied prospectively for four years by Geller et al. (19) had a mean time to recovery of 60 weeks, substantially longer than index episode recovery times observed in hospitalized manic adolescents by Strober et al. (18), and by Rajeev et al. (42), and they had a cumulative probability of recurrence of 70%,

also higher than the risk in teenage probands studied by Strober et al. (18) during a comparable period of follow-up, but in line with relapse rates reported in teens by Jaraim et al. (20). But given the caution just noted, whether long episode duration and high recurrence risk is a stable feature of very early onset disease or an artifact of the length and severity biasing of index episodes remains unknown. It also remains to be determined if those who develop the illness in early adolescence experience progressively shorter latencies to recurrence as they mature to adulthood. Although evidence of consistent shortening of cycle lengths with repeated recurrences of illness appears less robust than previously thought in adults (1,43,44), given that onset of bipolar illness prior to adulthood is associated with significantly greater genetic load (45), important biological and neuropharmacological differences associated with pediatric versus adult onset of bipolar illness may well exist. On the other hand, timing the onset and offset of episodes in inpatient samples (18,42) comprised exclusively of teens with low rates of ADHD/ODD comorbidity may be more reliable because confusion between persisting subthreshold symptoms of mania versus overlapping, symptoms of excitability, distractibility, negative mood, and lability from these chronically present comorbid states is minimal, and because the settings provide nursing observations that supplement parental reports of illness course. In short, the degree to which these differences in episode length are 'pure', suggesting truly longer periods of illness in children versus adolescents, or confounded by varying rates of comorbidity and differences in the quality of informant data remains open to question.

Given that the follow-up literature is sparse, little is known about predictors of episode recovery and relapse. Time to remission has been shown to be more rapid in subjects with pure mania at intake (18), and among those living with an intact biological family (46), and delayed in those with prior episodes (20) and with comorbid ADHD (29); increased risk of relapse has been associated with low maternal warmth (46), mixed polarity (18), lifetime history of depression (20), and longer duration of the index episode (20).

The Long-term Prospective Course of Bipolar Illness in Adults

Clinical morbidity

The importance of studying psychopathological disease course in children and youth over very extended periods is illustrated convincingly by findings on adults with bipolar illness showing how course patterns change markedly over time in ways that could not have been anticipated from outcomes observed early in the follow-up, and how overall morbidity, especially the frequency of subsyndromal symptoms, was far greater than anticipated. Specifically, in a long-term prospective follow-up study of unipolar depression (47-49), risk of recurrence declined steadily during the first five years of observation, suggesting a lessening of risk for future attacks, yet the risk and duration of episodes over the ensuing 10 years of follow-up were, in fact, stable, the cumulative probability of recurrence reaching 85% by year 15, and 92% by year 20. Similarly, long-term observation of adults with bipolar illness (1,50-52) has shown not only that continuous recurrences were the rule, but also that a substantial proportion of the follow-up time was characterized by symptoms of subsyndromal intensity, mainly depressive, and by very frequent shifts in polarity. In the case of BP-I illness (50), subjects were ill for nearly 50% of weeks throughout a mean of 12.8 years of prospective follow-up, manifested depressive symptoms in 30% of follow-up weeks, changed symptom severity level an average of 6 times per year, and shifted polarity an average of 3 times per year. Most surprising, however, was that adults with BP-II illness were equally impaired (51,52): they were ill an average of 54% of all follow-up weeks during a mean of 13 years of prospective follow-up, had 39 times more depressive than hypomanic symptoms, had an average 3.8 changes in symptom intensity level per year, and averaged 1.3 shifts in polarity each year, thus suggesting even greater overall greater chronicity compared to that observed in subjects with BPI-I illness. Even so, subjects with BP-II type illness were prescribed somatic treatment a substantially

lower percentage of time during and between affective episodes compared to those with BP-I illness.

Long-term course prediction

Recent long-term prospective, longitudinal studies of adults with bipolar illness have identified several features as having long-term prognostic significance. For BP-I and BP-II illness, greater chronicity, measured either as the percent of follow-up time in which a subject expressed full syndromal illness, or the percent of time with any affective symptoms, was associated with poor psychosocial functioning in the 5 years prior to intake, longer duration of the intake episode, depressive or mixed/cycling polarity of the intake episode, and substance use comorbidity (50-52). When chronicity was measured in terms of the persistence of manic or depressive disorder throughout year 15 of follow-up, 20% of BP-I adults were so classified, and this outcome was associated with poorer social functioning in the 5 years prior to intake, and alcoholism at the time of intake. Further analyses of these data also showed that the extent of depressive symptoms during the first two years of follow-up predicted depressive morbidity at the year 15 follow-up (53); that the number of manic but not depressive recurrences over 10 years of follow-up is increased significantly in subjects with a positive family history of mania (54); that recurrences are greater in subjects developing alcoholism *after* onset of affective illness compared to those with primary alcoholism (54); and that disease features including episode type (monophasic vs polyphasic), polarity sequence, and psychosis tended to persist in recurrences with poorer long-term prognosis associated with polyphasic compared to monophasic episodes, cycling episodes in which depression precedes mania, and psychosis (44,55,56).

Also of potential relevance to pediatric illness in view of the chronicity that has been documented in prepubertal patients, is evidence from a rigorously controlled longitudinal study of lithium prophylaxis in bipolar patients (57,58) that treatment failure is increased by greater number of episodes prior to treatment and the occurrence of subsyndromal symptoms during maintenance pharmacotherapy.

Psychosocial outcome

Studies of adults with bipolar illness (59-64) have consistently shown that impairment in multiple domains of psychosocial functioning persists after syndromal recovery. Moreover, in only a minority of patients is there return to premorbid levels of adjustment within one to 4 years after initial psychiatric hospitalization (59,63), and one study (65) suggests that recovery of role performance may be especially protracted when onset of illness begins prior to adulthood. These findings are compelling rationale for long-term prospective study of pediatric samples since the time course of recovery and predictors of long-term deterioration in psychosocial functioning in young bipolars has yet to be studied. Only by observing multiple domains of psychosocial adjustment prospectively as subjects mature developmentally and experience further recurrences of illness will it be possible to determine the magnitude and durability of impairment in youth, and elucidate how variability in length of recovery, number of recurrences, treatment exposure, and psychiatric comorbidity impact separately and additively on the course of psychosocial adjustment. Likewise, only through such long-term prospective study will it be possible to determine if sustained recovery of psychosocial functioning can protect against new episodes and general symptom morbidity.

Comorbidity

Both clinical and epidemiological studies indicate that bipolar illness is associated with high rates of alcohol and drug use, anxiety disorders, ADHD, and disruptive disorders (65-67). Theoretical and clinical relevance of these data to the study of pediatric samples follows from evidence that substance use in bipolar illness has been associated with earlier age of onset and

history of childhood hyperactivity (68,69), and, as noted above in the case of alcoholism, increase in the risk of recurrence in long-term follow-up (54).

The impact of comorbidity on the course of pediatric bipolar illness remains unknown, as hyperactivity has been shown to lengthen the time to episode recovery during lithium therapy in one study of adolescents (70), but not in another (30). Given that pediatric bipolars are soon to enter, or are passing through, the early period of risk for substance abuse, long-term follow-up of large cohorts is crucial for documenting how the level of impairment is magnified in the presence of comorbidity, the extent to which comorbidity rates increase with additional follow-up, and how such conditions impact impairment in psychosocial domains, long-term risk of recurrence, and response to naturalistically applied somatic and psychosocial therapies. Moreover, the effects of comorbidity in these samples will certainly need to be assessed in concert with other disease parameters rather than in isolation. Illustrative of the importance of doing so is a report by Carlson et al. (71), showing that age at onset of illness and history of childhood psychopathology were independently related to short-term functional and clinical outcome among patients with psychotic subtype of bipolar I illness, with onset under age 19 predicting persistence of illness and the presence of psychopathology during childhood predicting poorer functional outcome over a two-year follow-up.

Treatment as a mediating variable

Recent research illustrates the feasibility of applying novel statistical methodologies to long-term observational data to identify positive treatment effects in naturalistic clinical settings. For example, Leon et al. (72) showed that after controlling potential confounding variables that simultaneously influence disease outcome and treatment decisions (see 73-75 for background), unipolar depressed adults receiving high doses of antidepressant drugs were nearly two times more likely to recover from episodes of depression compared to those who received no somatic therapy. Similarly, in a study of maintenance effects of somatic treatment, Dawson et al. (75) showed that unipolar depressed adults remaining on the same antidepressant dose used to treat the acute episode received continuing benefit for at least eight months, and that an additional four months of prophylactic benefit was observable in subjects with three or more prior episodes. Analogously, for bipolar illness, Coryell et al. (76) showed that adults who received lithium while recovering from their index episode and who continued maintenance therapy had a lower risk of recurrence compared to those who discontinued treatment after recovery, and that lithium maintained its effectiveness in reducing time to recovery even when reintroduced following a period of discontinuation (77). Moreover, time to improvement during acute lithium therapy, while not differing as a function of familial loading for bipolar illness, was significantly slower among adults with a family history of major depression, an association that persisted throughout 11 mean years of prospective follow-up (78).

A further novel analytic technique that has been used in studies of adult affective illness (see 74, 79,80) that may be of particular importance to longitudinal studies of childhood bipolar illness given its tendency toward symptom chronicity, is multiplicative intensity modeling (81), a generalization of the 'hazard' in survival analysis which allows for multiple possible transitions over time among a set of defined states (whereas survival analysis examines a single transition in analyzing time to event occurrence); as such, it is ideally suited for the study of time sensitive clinical phenomena, such as fluctuating levels of symptom severity during the course of an affective episode. The broader appeal of this tool is that intensities can be compared statistically (e.g., do fluctuations vary by diagnostic subgroup?), can be plotted over time (e.g., do intensities decrease or increase over time by subtype of illness?), and studied in relation to time varying covariates (e.g., do current received levels of treatment differentially influence the frequency of transitions between wellness and clinical states?).

Relevance of such novel analytical methods to the naturalistic study of pediatric bipolar illness is apparent. Since we know that underutilization of treatments recommended by practice guidelines extends even to the most severely ill of adult bipolar patients (82), it is likewise of paramount importance to know how treatment seeking and clinician prescribing patterns correspond to illness course and morbidity in pediatric samples. Given ethical deterrents and other constraints to placebo controlled studies of the treatment of bipolar illness in pediatric patients (4), large-scale naturalistic, observational data sets on long-term trends in the types and intensity of somatic therapy received by young patients in various clinical settings, complemented by rigorous causal analyses of treatment effects, may be only the only comprehensive source of pharmaco-epidemiological and effectiveness data that will be available for refining clinical treatment guidelines in years to come. Moreover, flexibilities that are afforded by the naturalistic study of treatment effects potentially allow for examination of treatments separately (i.e., lithium, valproate), such that clinical outcomes of interest (e.g., time to new episode, speed of recovery, time to onset of sub-threshold symptoms) can be compared by illness subtype and category of treatments (e.g., Is valproate superior to lithium in preventing recurrences among subjects with mixed episodes, as suggested by adult studies of BP disorder? Do treatments vary in effectiveness in prepubertal versus adolescent patients? Do these treatments reduce the fluctuation of symptom intensities in patients with continuous morbidity?). This type of approach to the quantitative study of treatment effectiveness remains underutilized needed in child psychiatry.

Essential Requirements and Study Aims in a Longitudinal Study of Pediatric Disease

It can be seen how accumulating knowledge of bipolar illness in adults as highly recurrent with continuous morbidity of moderate to severe intensity brings into much sharper focus the multiple aims and overarching scientific rationale of a long-term study of pediatric forms of the disease. Early onset is presumed to have unique genetic and neuropharmacological properties with developmentally pernicious effects, but our science is limited when viewed against the backdrop of the growing adult literature. Only through systematic, fully structured, prospective follow-up of clinically diverse cohorts through the multiple cycles of recurrence and recovery as subjects mature from childhood to adulthood can we illuminate the effects of disease progression across developmental stages, validate clinical subtypes, and identify reliable predictors of outcome and treatment mediators of course.

Methodological requirements

If a comprehensive prospective study of pediatric bipolar illness is to have broad generalizability and rigorous scientific validity, it must ideally have the same core methodological features embodied in recently reported studies of adults with affective disease. These include,

- a. uninterrupted, long-range follow-up that tracks probands across transitional developmental stages;
- b. ascertainment of a large, clinically and demographically heterogeneous cohort recruited from multiple sources;
- c. use of assessments that are structured and anchored to standardized diagnostic criteria;
- d. high intensity, frequent contacts with both subject and parent informants, and use of teacher informants, as well, to document effects of the illness across multiple domains of functional relevance. Also worthy of consideration, especially since juvenile patients, preadolescents in particular, exhibit chronic and rapidly fluctuating mood states, is incorporating in observational designs the use of ecological valid methods

of data collection wherein programmable handheld computers, pagers, or watches are signaled throughout the day at predetermined intervals to record behavioral and affective states in subjects in real time.

- e. continuous recording of the type, dose, and duration of somatic therapy, and type and frequency of psychological treatments received throughout the follow-up that is correlated with simultaneously obtained ratings of psychopathological symptom intensity and psychosocial functioning across multiple domains.

With this body of research as a point of departure, we offer the following proposed aims for the long-term prospective longitudinal study of early onset bipolar disease:

1. **Describing long-term naturalistic course patterns of episode recovery, recurrence, and chronicity.** Long-term prospective observation of cycles of recovery and recurrence as subjects move from childhood to adolescence, and then to adulthood, will (a) document the risk of chronicity; (b) identify long-term course typologies based on episode frequency and the duration of well periods; (c) permit comparison of prepubertal- and pubertal-onset subgroups in regard to long-term course and functional outcome, as well as the effects of puberty on expression of disease phenomenology; (d) illuminate differential outcomes of the BP subtypes as well as rates of conversions from BP-NOS to BP-I and BP-II, and from BP-II to BP-I; and (e) document the frequency subsyndromal manic and depressive states over the longer-term course of illness in early onset subjects.

Since the proper boundary for delimiting the bipolar phenotype among preadolescents is uncertain, we believe that observational studies need to be broadly conceived in regard to sample ascertainment to have the greatest heuristic potential, not only for shedding light on long-term morbidity across a spectrum of clinical phenotypes, but also for informing the validation of varying descriptive phenotypes, as recently proposed by Leibenluft et al. (83). Thus, comparative long-term prospective study of children who exhibit extreme, persistent negative emotional, hyperactivity, and hyperarousal but who lack cardinal features of mania; children with classic euphoric mania; children with classic manic features of only very brief duration; and children with depression from bipolar ancestry represent the ideal spectrum of subjects for inclusion in such an effort, that would ideally also include measurement of validating parameters such as family history, and neurocognitive and neuroimaging endophenotypes.

2. **Identifying predictors of outcome and course trajectories.** Observing these subjects through multiple recurrences over long-term follow-up will determine if different predictors of course emerge over time, and if these variables are similar to, or different from, those identified in adult studies.
3. **Describing the course of psychosocial functioning.** Long-term prospective follow-up will yield critically important data on the cumulative effects of pediatric bipolar illness on psychosocial adjustment and suicidality, as well as interdependencies between symptom and psychosocial morbidity as subjects mature. Only by describing the prospective course of psychosocial adjustment and suicidal behavior during these critical periods of development can light be shed on the latency to improvement of psychosocial functioning following episode recovery, variations in these trends by age, subtype of illness (BP-I vs. BP-II vs. BP-NOS) and other pertinent clinical features, and features that distinguish subjects with long-term social deterioration from those who maintain adequate adjustment.
4. **Comorbidity.** Extending the time of follow-up of pediatric cohorts is directly relevant to risks and determinants of comorbidity associated with bipolar illness, especially

drug and alcohol abuse and anxiety disorders, as well as the long-term effects of comorbidity present at intake, including anxiety disorders, ADHD, and disruptive disorders.

5. ***Treatment as a Mediating Variable.*** Observing long-term trends in the use of naturalistically applied pharmacological and psychosocial therapies in children and youth can illuminate effects of these treatments in mediating outcomes of importance. Importantly, rigorous, long-term naturalistic prospective study of treatment effects in pediatric bipolar illness extended into adulthood can test the hypothesis that mechanisms operating in treatment response are not fixed, but rather may be time or period sensitive (i.e., responsiveness may increase or decrease as subjects mature). The broader power of this approach is that examination of treatment effectiveness is not limited to discrete points in time; moreover, if effectiveness of these therapies can be demonstrated the data can then simultaneously address the question of whether this population receives lower than the optimally recommended levels of acute and preventative care, a matter of immense clinical and public health importance. Given the many complications that plague the design and execution of placebo-controlled studies of bipolar illness in youth, long-term observational data on trends in the types and intensity of somatic therapy received by bipolar youth in the community, complemented by planned rigorous causal analyses of treatment effects, will provide pharmacoepidemiological data of immense clinical and public health importance.

Clearly, observations of this type are not adequate substitute for the rigorous control afforded by the randomized placebo controlled clinical trial. Still, statistical methods (73-75) to deal with the problem of 'confounding by indication' (84), in which historical and clinical factors influence treatment decisions, have been adapted successfully for studying the impact of lithium maintenance therapy in the long-term prevention of recurrence in adults with bipolar disorder (76), and the impact of antidepressants and lithium in preventing recurrence and reducing the frequency of symptomatic transitions over time in unipolar depression and bipolar disorder (74,75,79,80). Models examining treatment effects can include such potential confounds as treatment intensity, polarity and duration of the episode, prior episodes, etc., as factors that simultaneously influence disease outcome and differentially influence treatment decisions (see 74 and 75 for illustration). The survival regression models that derive from these analyses then allow for stronger causal inferences concerning treatment effects. Moreover, flexibilities that are afforded by the naturalistic study of treatment effects allow observational studies to examine treatments separately (i.e., lithium, valproate), such that clinical outcomes of interest (e.g., time to new episode, speed of recovery, time to onset of sub threshold symptoms) can be compared by illness subtype and category of treatments (e.g., Is valproate superior to lithium in preventing recurrences among subjects with mixed episodes, as suggested by adult studies of BP disorder?). This approach to the quantitative study of treatment effectiveness is sorely needed in child psychiatry since it is exceedingly unlikely that placebo controlled study of these questions will be undertaken in the foreseeable future; nevertheless, the issues are confronted daily in the clinical practice of pediatric psychopharmacology. To the degree that course differences can be shown as a function of treatment exposure, long-term observational study of juvenile bipolar disorders may assist in developing new guidelines for their long-term management.

Conclusions

It will not be possible to understand the cumulative and enduring developmental effects of pediatric onset of bipolar illness, or the resiliencies and protective processes that operate in affected children, without truly long-term, prospective study of the course of illness and treatment patterns in large, diversely ascertained cohorts. The range of hypotheses that can be tested, including opportunities to identify discriminating predictors of favorable versus

negative long-term outcomes as well as the mediating effects of naturalistically applied treatments, underscores the versatility of this research perspective in bridging basic clinical and pragmatic objectives, and its broad scientific and public health significance. Our proposal is certainly not exhaustive; others will find yet additional avenues for fruitful study.

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