Paradigm Shift: Preliminary Clinical Categorization of Ultrahigh Risk for Childhood Bipolar Disorder to Facilitate Studies on Prevention

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Recent epidemiologic data suggest an approximate 2.5% incidence of bipolar spectrum disorder in adolescents,[1,2] and retrospective data in adults (mean age = 42 years) in the United States suggest that the onset of bipolar illness occurs in childhood prior to age 13 in one-fourth to one-fifth of cases.[3,4] The data converge with a variety of other studies in clinical populations indicating that pediatric-onset bipolar disorder is common, highly disabling, difficult to treat,[5–10] and prone to relapse.[11–20] Moreover, one-third of well-diagnosed children during an 8-year follow-up of naturalistic treatment in the community never received any of the recommended pharmacologic treatments for bipolar disorder.[16]

Given the very considerable morbidity and dysfunction associated with childhood-onset bipolar illness, early identification and treatment remain a very high but elusive priority. Childhood-onset illness is associated with a more adverse outcome in adulthood than adult-onset illness.[3,4,21,22] In addition, the duration of the time lag to first treatment is an independent risk factor for a poor outcome in adulthood.[3] More specifically, acute response rates to the gold standard mood stabilizer lithium are reduced with increased prior episode burden, suggesting that undiagnosed or poorly treated adolescent bipolar disorder reduces the response for successful outcome for adults treated with lithium.[23] The public health implications of nonresponse, general morbidity, and financial costs are staggering: $11,720 for persons with a single manic episode versus $624,785 for those with nonresponsive illness.[24]

Further confounding attempts at early intervention are the paucity of studies delineating optimal treatment approaches even for children meeting full criteria for bipolar I disorder.[25–27] While quetiapine, aripiprazole, and risperidone have been approved by the US Food and Drug Administration (FDA) for children from 10 to 17 years of age with bipolar I disorder, olanzapine has been approved for adolescents aged 13–17, and lithium "grandfathered" in children older than 12, treatment sequences and algorithms have not been well studied and depend on expert opinion.[25,26,28] Treatment for children with bipolar II disorder and bipolar disorder not otherwise specified (NOS) has rarely been studied.

A recent study sponsored by the National Institute of Mental Health found that the atypical antipsychotic risperidone was substantially more effective than either lithium or divalproex in the treatment of childhood-onset mania,[29] yet tolerability problems were seen in the domains of weight gain, prolactin increases, and sedation. Comparative study with other better-tolerated atypical antipsychotics is now an urgent but completely unmet need.

We suggest that high risk and ultrahigh risk for childhood-onset bipolar disorder can already be preliminarily delineated for children on clinical grounds prior to the ascertainment of other more slowly forthcoming neurobiological measures. In this fashion, information about those with ultrahigh-risk status can be utilized to begin to explore the effectiveness of approaches to primary and secondary prevention in young children.

This strategy could lead to an iterative process in which clinical and biological markers of illness onset and progression could then be reassessed as the field matures and more data become available. As more neurobiological markers begin to be assessed and validated, the clinical categorizations of these early provisional high-risk and ultrahigh-risk children could be revised accordingly. Finally, these same predictors of onset of illness and course of illness markers could be reinvestigated for potential prediction of individual response to individual treatments in those who do become ill.

Recent data suggest that parental report of treatment outcome is an excellent alternative approach to treatment outcome rated by other trained observers. This approach also converges with the data that parental reports on the symptoms necessary for a diagnosis of childhood-onset bipolar illness are more reliable and valid than those from teachers or the young children themselves,[30–32] and repeated parental report of symptoms is helpful in making a bipolar diagnosis.[33] Greater reliance on parental evaluations would minimize costs and allow the development of Web-based comparative effectiveness trials.

Parental illness variables are one set of clear risk factors for early-onset bipolar disorder. Parental history of bipolar disorder increases the risk of bipolar disorder in the offspring to approximately 20% and for any affective disorder or psychiatric illness even farther.[11,34] If, however, both parents are affected (one with bipolar disorder and the other with either bipolar or unipolar disorder), the risk for an affective disorder in the offspring increases to about 70%.[35] If, in addition, one or both of the parents were also actively ill, this occurrence would very likely increase the rate of psychiatric disorder even further in the offspring,[36–38] as would a positive parental

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history of an alcohol or substance abuse disorder or a serious suicide attempt.[36–38]

Environmental risk factors for childhood bipolar disorder have also been identified and include preterm delivery,[39] childhood adversity,[40–42] the presence of other childhood psychiatric conditions, and prodromal symptoms or a bipolar disorder NOS diagnosis.[6,8] Thus, a case can be made that a preliminary delineation of high- and ultrahigh-risk categories based on parental, environmental, and symptom variables could be made on clinical grounds now that would allow the initiation of studies of primary (prior to illness onset) and secondary (after first symptoms/episode) preventive interventions in those at highest risk.

Given this type of provisional very high-risk status (rating sheet available upon request), particularly if the child were already prodromal or syndromal with bipolar disorder NOS, the idea of active treatment interventions becomes compelling from both a clinical care and an ethical perspective. If one begins to utilize the comparison of 2 putatively active, safe, and well-tolerated pharmacologic or psychotherapeutic modalities in clinical trials, parents would be highly likely to want their children to participate in such studies.[43] Such preventive interventions could include systematic exploration of different psychotherapeutic approaches and pharmacologic agents, including vitamins, a micronutrient formula (such as EMPowerplus), omega-3 fatty acids, and *N*-acetylcysteine.

Finally, this study of primary and secondary prevention in open studies in childhood-onset bipolar disorder, initially based only on clinically derived factors, also opens the possibility of later utilizing these same existing cohorts to facilitate the definition of neurobiological markers of onset risk, course of illness, and ultimately response to treatment prediction. A large number of medications are already being widely utilized in the community, yet the long-term outcome of the use of these agents alone or in combination—effectiveness, tolerability, or prediction of individual response—has rarely been systematically studied.

As argued by many investigators, the utilization of practical clinical trials could not only accelerate the generation of clinically useful information but also potentially accelerate the development of clinical and biological markers.[44–48] The traditional gold standard, a randomized, controlled clinical trial with a placebo parallel group, is ideal for the generation of FDA-approval status and licensing of a drug but is extraordinarily expensive, cumbersome, and deficient in generating either optimal clinical treatment strategies or markers of clinical response.[48]

We are suggesting that large numbers of subjects could be identified and studied in the community as in clinical trials in cancer therapeutics but at a markedly reduced cost. Both risk status and follow-up of the effectiveness and tolerability of the interventions would initially be highly dependent on parental report in order to free clinicians in busy clinical practices to be able to participate with a minimal time commitment.

Multiple sites and international consortia are currently examining formal, double-blind methods of evaluating potential neurobiological markers of bipolar illness, onset, progression, and response to treatment, but these efforts are using highly diverse measures and methods, are inconsistent across sites, and are extraordinarily expensive. Even if a whole host of neurobiological markers becomes available in the not-too-distant future, this would still leave the field at a loss as to how to begin to explore potential primary and secondary preventive treatments and to pursue tertiary preventive treatment strategies once full-blown illness has already been identified.

The current proposal could help overcome many of these logistical, methodological, recruitment, and financial obstacles. Large numbers of young subjects at ultrahigh risk could be rapidly identified in the community, and if parents desired it, enrolled in open preventative comparative clinical trials of 2 very safe modalities in clinical practice settings. Dispensing of interventional agents would be accompanied by basic psychotherapeutic and behavioral recommendations (eg, good sleep hygiene, exercise and diet recommendations, and basic stress coping skills) to enhance care in all participants.

Participating academic centers could simultaneously validate parental ratings with other more detailed measures that they are using and add new candidate neurobiological markers for investigation. As the subgroup of high-risk children who become syndromal is treated in the same clinical practice settings, the risk markers could then be reevaluated for their potential prediction of individual clinical response to individual drugs. An iterative process would take place as preliminary clinical treatment response data would be replicated and putative predictors of response augmented by new neurobiological candidates as new information became available.

Thus, rather than having an expensive, time-consuming sequence of examining possible markers in initial double-blind, placebo-controlled studies and then performing cumbersome validation studies (which may never be adequately funded), we suggest a more accelerated and streamlined project starting with children readily identified clinically to be at very high risk and preliminarily evaluating the safest preventive treatments and then the safest acute treatments in those who become ill. This paradigm shift could rapidly produce a wealth of preliminary data on effectiveness and safety of early preventive and treatment strategies while facilitating the acquisition, revision, and accretion of new clinical and neurobiological markers.

Drug names: aripiprazole (Abilify), divalproex sodium (Depakote and others), lithium (Lithobid and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

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