

# The Early Natural History of Bipolar Disorder: What We Have Learned From Longitudinal High-Risk Research

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Longitudinal high-risk research has provided convergent evidence that major mood and psychotic disorders often develop from nonspecific antecedents in predisposed people over time and development. For example, bipolar disorder (BD) appears to evolve from nonspecific childhood antecedents, including anxiety and sleep problems, followed by adjustment and minor mood disturbances through early adolescence, culminating in major mood episodes in later adolescence and early adulthood. Therefore, the current cross-sectional symptom-based diagnostic approach requires rethinking: it considers neither the familial risk nor the longitudinal clinical course, with the consequence that the early stages of illness are not recognized as belonging to the end-stage disorder. Emerging evidence of identifiable clinical stages in the development of BD has tremendous potential for early identification, development of stage-specific treatments, and advancing our understanding of the pathophysiology associated with illness onset and progression. The clinical staging model also has direct implications for the optimal organization of clinical services for high-risk youth. Specifically, specialty psychiatric programs are needed that break down traditional institutional barriers to provide surveillance and timely comprehensive psychiatric assessment during the entire risk period, from childhood through to early adulthood. In this regard, the development of specialty psychiatric programs aiming to identify youth in the early stages of evolving psychosis are substantially ahead of services for youth in the early stages of evolving major mood disorders.

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### Highlights

- Prospective longitudinal studies of the children of affected parents have provided an important opportunity to describe the early natural history of BD.
- New evidence supports a clinical staging model that, if replicated, will improve early detection and provide a conceptual frame for early intervention and neurobiological research.
- Implications of completed high-risk research point to the importance of a developmental approach to psychiatric diagnosis and highlight the need for specialty programs for youth at high risk of major mood disorders.

**Key Words:** *high-risk studies, bipolar disorder, clinical course, natural history, clinical staging, heterogeneity, early diagnosis, treatment*

In this paper I will review the key findings related to the early natural history of BD from selected published high-risk studies and discuss the contribution of our (my colleagues and me) high-risk research carried out during the past 15 years. I will then go on to discuss the implications of this research for diagnosis, treatment, service organization, and future research of people at high risk for BD. The findings gain some additional weight when placed side by side with the high-risk studies of prepsychotic youth led by Dr McGorry and colleagues<sup>1</sup> in this issue.

As a starting place, it might be helpful to understand the beginnings of my own interest in high-risk research. During residency training in child and adolescent psychiatry, it became apparent to me that patients manifesting seemingly different illnesses met DSM diagnostic criteria for the same disorder. This raised the question as to how all of the youth diagnosed with major depressive disorder could suffer from the same illness, when there were obvious differences in the clinical course, family history, and treatment response between these so-called depressed youth? The other observation that struck me was the accumulation of different diagnoses in the same person over time and development. Could a single child really be so unlucky as to have many different evolving or concurrent psychiatric problems; that is, comorbid attention deficit disorder, pervasive developmental disorder, anxiety disorder, conduct disorder, and BD? Finally, there was the feeling that one was just beginning to see the full manifestation of the underlying illness, when the patient would be either discharged from care or lost to follow-up having surpassed the milestone of age 16 years.

These observations led me to the conclusion that the only way to understand the early natural history of BD was to prospectively study youth at high risk. Such an approach would help us to reliably differentiate the phenotypic spectrum of BD from other problems (psychiatric and nonpsychiatric) with prominent mood symptoms. Further, this research would need to span childhood, adolescence, and early adulthood to map the complete natural history and determine which early manifestations were continuous with the end-stage illness.

Many major psychiatric disorders onset during adolescence.<sup>2</sup> BD is associated with the highest estimated heritability of all major psychiatric disorders, including schizophrenia.<sup>3,4</sup> Therefore, the offspring of parents carefully diagnosed with BD are themselves at elevated risk for developing BD. Prospective longitudinal high-risk studies allow for the identification of vulnerability traits and the differentiation of these from burden of illness (for example, recurrent episodes and

psychosis) and treatment effects. Further, longitudinal high-risk studies allow us to map the early natural history of the illness; identifying any antecedent conditions associated with later full-blown disorder and characterizing the prodrome or the first reliable clinical manifestations of impending illness onset. A good understanding of the early stages of illness development allows for the identification of critical periods for effective early intervention and perhaps prevention. Finally, given the instability of psychiatric diagnoses in unselected clinically referred children,<sup>5,6</sup> high-risk studies markedly increase the likelihood that one is really observing the early stages of, in this case, BD, rather than the manifestations of another psychiatric disorder or behaviourally, sociologically, or psychologically based emotional disturbance.

### Findings From Published High-Risk Studies

The validity of the findings from high-risk research rely on the assumption that the parent actually has the disorder under study, and therefore the critical starting place for this work is with carefully diagnosed parents. Given the well-discussed limitations of symptom-based DSM<sup>7-9</sup> and similar diagnostic systems that emphasize cross-sectional assessment, heterogeneity of parent samples is a major challenge in interpreting the findings from high-risk studies. In addition, reported high-risk studies differ along other methodological lines, including: variability in the expertise and training of those conducting offspring assessments; approach to offspring assessment (parent report, compared with direct interview), assessment at one time point or multiple points over time and variability in the duration of follow-up; degree of psychiatric illness in the nonproband parent (that is, assortative mating); and whether or not there was a comparably assessed control group.

There are now several published studies describing psychopathology among the offspring of parents with BD.<sup>10-12</sup> Most of these studies are cross-sectional in nature, providing a snapshot of lifetime psychopathology. Few studies have a significant longitudinal prospective follow-up component. One of the earliest such studies was reported by Akiskal et al<sup>13</sup> and described psychopathological outcomes in the referred juvenile family members (mostly adolescent) of patients with BD (parents or older siblings) based on expert comprehensive psychiatric assessments during a 3-year period. The major findings from this study included the observation that neurotic symptoms and adjustment disorders were not uncommon in the early childhood history of the high-risk subjects, and that BD most often manifest as a depressive episode or attenuated mood disorder (dysthymia or cyclothymia). Further, full-blown hypomania or mania was not observed until after age 13 years. The strengths of this study<sup>13</sup> include the fact that the research team had extensive clinical knowledge of the proband adult family member, as well as the systematic use of conservative diagnostic criteria (Feighner's criteria consistent with DSM-III) by an

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#### Abbreviations used in this article

ADHD	attention-deficit hyperactivity disorder
BD	bipolar disorder
DSM	Diagnostic and Statistical Manual of Mental Disorders
SUD	substance use disorder

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experienced psychiatrist with extensive subspecialty training in mood disorders for proband and high-risk subject assessment; that is, family members were assessed in a comprehensive psychiatric interview considering all available clinical material, rather than by a trained interviewer using a symptom checklist.

A second longitudinal study was reported on by Hammen et al<sup>14</sup> in 1990. This study systematically evaluated the offspring of mothers with depression, BD, chronic illness (mostly diabetes), and no illnesses. Mothers with BD were identified through both in- and outpatient programs and met diagnostic criteria for either BD I or II. The offspring were, on average, in their early adolescence. During the 3-year follow-up period, offspring of mothers with BD tended to have an intermediate risk of lifetime psychopathology, falling between that of the offspring of those with depression (highest risk) and the other 2 comparison groups. Most of the early childhood psychopathology among the BD risk group was related to anxiety disorders and minor depressions, while major mood disturbances began after age 12 years. No hypomanic, manic episodes, or cyclothymic disorders were diagnosed, although it was felt that subsyndromal mood lability and activation symptoms were present in a few of the BD high-risk offspring.

A Dutch longitudinal study<sup>15</sup> of the offspring (aged 12 to 21 years) of largely community-identified parents with BD was started in 1997. The parents were interviewed to confirm their diagnosis and met DSM-IV criteria for either BD I or II. During a 5-year prospective observation period, there were 3 assessments (baseline, 14 months later, and an additional 40 months later) using the Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime (commonly known as KSADS-PL) interview format. During the study period, it was reported that high-risk offspring (compared with the general population) had an elevated rate of lifetime psychiatric disorders, including mostly major mood disorders, minor mood and adjustment disorders, and anxiety disorders and SUDs.<sup>16</sup> The rate of ADHD and disruptive behavioural disorders was only 5% and 7%, respectively. The majority of mood disorder was accounted for by depressive disorders (44/53 diagnoses). Among offspring who met lifetime criteria for BD, the first mood episode was depressive in polarity in 12 out of 13 subjects, and the average age of onset was 13 years (range 9 to 22 years). The average latency between the first depressive episode and the first activated episode (hypomania or mania) was 4.9 years. There was no subject who met full-blown criteria for mania, hypomania, or cyclothymia before age 12 years.

Finally, an interesting longitudinal prospective study<sup>17,18</sup> of the offspring of Amish parents with BD I has focused on mapping the earliest signs and prodromal symptoms of BD. The parent probands were conservatively diagnosed for participation in a separate genetic study. At the 10-year mark, these investigators reported that specific clinical features were significantly more frequent in high-risk offspring, compared

with control subjects, and that there was symptom progression during development from sensitivity, fearfulness, and low energy to high energy, sleep disturbance, excessive talking, and problems thinking and concentrating. In addition, there was evidence that these symptoms would occur in mini-clusters rather than being chronically present. This finding reemphasized the episodic nature of BD, a classic hallmark not present in recent clinical descriptions of patients with putative pediatric BD.<sup>19–21</sup> Further, there was a complete absence of the proposed prepubertal bipolar phenotype, characterized by chronic mood instability, explosive temper and aggression, irritability, and comorbid ADHD and pervasive developmental disorder.<sup>21</sup>

Despite differences in the identification and recruitment of families and methods for assessment of the offspring, the clear and convergent finding from these studies is that offspring of parents with well-characterized BD meet lifetime diagnostic criteria for a wide range of psychiatric symptoms and disorders. Major mood episodes typically do not onset until at least adolescence and most commonly debut as a major depressive episode. Longitudinal high-risk studies, starting with carefully diagnosed parents, do not find diagnosable episodes of hypomania or mania in childhood, although there may be subthreshold symptoms. Further, there were no reported cases consistent with the pediatric bipolar phenotype, discussed largely in US clinically referred samples of children unselected for family history.<sup>22,23</sup>

The highly replicated findings on nonspecificity of psychopathology, early in the childhood and early in the course of illness, is hard to reconcile given that these children were selected for a specific genetic risk of BD. According to the prevailing concepts, children of parents with carefully diagnosed BD should not display such a multiplicity of diagnoses. For example, from adult studies<sup>3,24,25</sup> we assume that disorders segregating in family members of a BD proband are limited to major depression (especially recurrent), cyclothymia, BD (I and II), and schizoaffective BD (episodic). Therefore, we set out to address the possible origins of this apparent contradiction.

## Our High-Risk Research

Initial speculation by my colleagues and me was that the broad spectrum of psychopathology in high-risk children might reflect a combination of assortative mating effects (varying degrees of different psychiatric illnesses in the nonproband parent) and heterogeneity of BD in the parents. To address these potential confounding factors, in 1995, my colleagues and I embarked on a high-risk study<sup>26</sup> which limited inclusion to well-characterized families. Specifically, one parent with BD was diagnosed by a semi-structured research diagnostic interview administered by an experienced research psychiatrist and confirmed on blind consensus review by at least 2 additional research psychiatrists, blind to the families and using all available clinical material. The other parent had to be psychiatrically well. As many

patients and family members were involved in genetic studies, we had extensive family history information.

We also treated many of the parents and had extensive clinical information about their course of illness and response to treatment,<sup>26</sup> which made it possible to determine if the parents had an unequivocally response or nonresponse to long-term lithium treatment in accordance with a research protocol.<sup>27</sup> Mounting evidence suggested that a good response to lithium prophylaxis (complete and sustained remission on therapeutic lithium following a highly recurrent untreated course) identified a more homogeneous subgroup of patients with BD with stronger genetic loading, and specific neurobiological and genetic findings.<sup>28,29</sup> Offspring were assessed at baseline and annually by a child and adolescent research psychiatrist blind to familial affiliation and were reviewed blindly in consensus meetings by at least 2 additional experienced research psychiatrists, and were required to meet full DSM criteria for psychiatric diagnosis.

The initial main finding from this high-risk research was the unexpected replication of the observation of a broad range of lifetime psychopathology among both high-risk subgroups (offspring of lithium responders and nonresponders).<sup>26,30</sup> Clearly, the lack of specificity in psychiatric outcomes could not be adequately explained by assortative mating or heterogeneity, as we had initially speculated. However, in our observations, there were certain key differences from the reports in the clinical literature that also supported the findings from other longitudinal studies described above. Namely, we neither found an elevated risk of ADHD or disruptive behavioural disorders in the high-risk cohort, compared with the general population, nor observed any prepubertal hypomanic or manic episodes.

Since 1995, we have continued the high-risk research increasing the sample of prospectively assessed offspring and recruited a similarly assessed control group of offspring from families with 2 unaffected (for major psychiatric disorders) biological parents. There have been several key observations from these studies that have helped to clarify our initial findings. First, we replicated the finding of an increased risk of nonmood psychiatric disorders in both high-risk groups and observed that, while ADHD was not elevated in the high-risk sample as a whole, it was differentially present among the offspring of lithium nonresponders, along with other neurodevelopmental manifestations described previously in children at risk for psychotic disorders, including Cluster A traits and learning disabilities.<sup>31</sup>

Second, an analysis of the course of mood disorders in the high-risk offspring, based primarily on prospectively described episodes and generally free from confounding effects of treatment, showed that major mood episodes started to onset at around age 12 years (not before) and continued to onset through the observation period. The mean age of onset was mid-adolescence, and the first major mood episode and the first few recurrences were almost always depressive in polarity; activated episodes were typically seen several years

later. Further, there was no single observed case of prepubertal mania or case consistent with the proposed pediatric bipolar phenotype.<sup>32</sup>

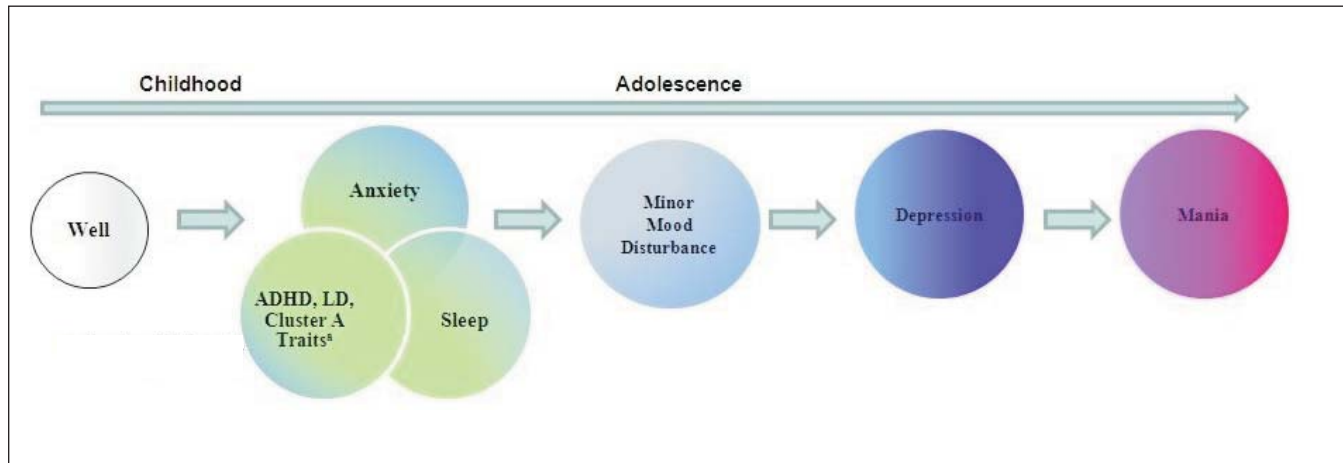
Third, we made the novel observation that in people who developed full-blown BD (I or II), there was a sequence or progression of psychopathology starting with nonmood disorders in childhood, evolving into minor mood disorders and sensitivity to stress (adjustment disorders) in early adolescence, and finally depressive episodes followed by activated episodes in mid- to late-adolescence. SUDs tended to onset at the same time or following the first major mood episode. The early nonmood antecedents differed between high-risk subgroups, both manifesting anxiety and sleep disorders, but only the offspring of lithium nonresponders manifest neurodevelopmental antecedents.<sup>33</sup> Among high-risk offspring, having an anxiety disorder in childhood was associated with more than a 2.5-fold increased risk of developing a major mood disorder, compared with the risk in those without a history of childhood anxiety disorder.

Fourth, the nature of the course of mood disorders (episodic, compared with nonepisodic) was associated with the nature of the clinical course in the parent,<sup>31</sup> and we reported evidence of a selective response to mood stabilizer monotherapy in affected offspring associated with the nature of the clinical course (episodic, compared with nonepisodic) and the history of response in other adult family members.<sup>34-36</sup>

Finally, we confirmed that neuroimaging<sup>37,38</sup> and neurocognitive findings<sup>39,40</sup> present in clinical patient samples did not appear to be present in the high-risk subjects, suggesting that these are likely related to the burden of illness (duration of illness, psychosis) and treatment effects, rather than representing vulnerability traits or endophenotypes in the offspring of parents with well-characterized BD.

### Resolving the Apparent Discrepancies

When one puts together the findings from studies of the children of parents with lithium-responsive and lithium-nonresponsive BD, seemingly discrepant reports from the child and adult literature can be resolved. That is, heterogeneity of BDs in parents appears to explain why ADHD and other cognitive difficulties are observed in some high-risk offspring studies and not in others. In our studies, ADHD and cognitive difficulties were observed among a subset of the offspring from lithium-nonresponder families, but not among the offspring of lithium responders. Therefore, cognitive problems in the offspring may form part of a neurodevelopmental phenotype related to the elevated risk of psychotic disorders in the adult relatives in these families. Other evidence supports this hypothesis; specifically, Meyers et al<sup>6</sup> and Carlson<sup>41</sup> have reported that there is a relatively high conversion rate from what is initially diagnosed as mania into psychotic disorders, especially in adolescent patients with a history of psychopathology in early childhood. Further, there is substantial literature supporting a neurodevelopmental phenotype predating psychotic

**Figure 1 Clinical stages: development of BD in high-risk offspring**

<sup>a</sup> Offspring lithium nonresponder only  
LD = learning disability

disorders in children,<sup>42,43</sup> as well as an overlap in genetic findings for schizophrenia and a subgroup of patients with BD with prominent psychotic features.<sup>29</sup>

Heterogeneity of BD accounts for striking differences in the clinical course of mood disorders (episodic, compared with nonepisodic) between high-risk subgroups.<sup>44</sup> The nature of the clinical course has been recognized as a predictor of response to specific mood stabilizers.<sup>45–47</sup> Further, the nature of the clinical course is one of the characteristics differentiating BD subtypes and is related to differential pathophysiological correlates, family history, treatment response, and prognosis.<sup>48–52</sup> In our experience, customizing treatment by incorporating the clinical profile of the individual patient (for example, nature of the clinical course, the family history of psychiatric disorders, and the familial response to treatment) into the selection of the mood stabilizer for that patient improves their outcome dramatically, compared with outcomes from randomly chosen treatments listed in generic treatment guidelines.<sup>35,36,53</sup>

The other key finding from the high-risk research is the evidence that the early natural history of BD unfolds in a series of predictable clinical stages. It appears likely that nonspecific psychopathology in children at specific genetic risk of BD represents the early clinical manifestations of BD, rather than unrelated psychiatric problems or so-called comorbid illnesses. The model we are currently studying is illustrated below using the concepts articulated by Dr McGorry and colleagues<sup>1</sup> regarding the early clinical stages of schizophrenia (Figure 1).

Our longitudinal data show that the proposed sequence of clinical stages is followed by most of the high-risk offspring who have developed BD, but not all of these people have manifested every stage (for example, join the sequence of stages at

any place but then follow the same sequence).<sup>33</sup> Studies of adult patients may have missed these early clinical stages, as they relied on retrospective recall from patients who may not have remembered or did not associate these nonspecific antecedents with the subsequent mood disorder. There may be alternative explanations for the earlier clinical stages and ages of onset of major mood episodes in later generations that require systematic study (see below). In the meantime, clinical staging is a major new finding that should have a striking impact on our current clinical practice, service organization, and the direction of future research.

We have also observed that the major neuroanatomical and neurocognitive findings present in patients with established illness are downstream effects related to burden of the illness and seemingly not biological vulnerability markers. We have also reported that psychotic symptoms are an important aspect of the burden of illness and are associated with neurocognitive dysfunction early in the course of established illness.<sup>40</sup> These findings provide the hope and possibility that early effective intervention may stop or attenuate the progression of BD and strikingly improve the outcome and quality of life for high-risk people at a critical stage in their development.

### Diagnostic and Treatment Implications

As mentioned in the Introduction, the DSM diagnostic criteria for mood disorders are so broad as to be relatively meaningless for predicting course, outcome, and treatment response for individual patients. That is, patients sharing the same diagnosis in DSM constitute a highly heterogeneous group, in part because evidence used routinely in medical diagnosis (clinical course, family history, and treatment response) are not considered in the diagnostic formulation in psychiatry. Even in the case of BD, phenotypic complexity

and genetic heterogeneity are important issues with identifiable subgroups of patients having clear differences in family history of illness, familial treatment response, clinical course, response to prophylaxis, and in their neurobiological and genetic associations.<sup>4,29</sup> As pointed out by Grof et al,<sup>54</sup> the traditional diagnostic methods in psychiatry are over 100 years old and were based on observations of end-stage disorder in very ill hospitalized patients. These diagnoses were assumed to be stable and were modified by committees rather than by solid research findings.

Further, the categorical diagnostic approach does not allow for refinement of diagnosis very early in the course, before the manifestation of full-blown illness. Evidence that BD evolves in people at risk, from nonspecific to specific psychopathology and from mild to more severe mood episodes, suggests that identifiable clinical stages may be a valid and helpful way of conceptualizing the early natural history of BD. These observations add to those in clinical samples of adult patients with BD<sup>55,56</sup> and to the landmark work of McGorry and colleagues (see Phillips et al<sup>57</sup>) in characterizing the early course of psychotic disorders. Moreover, this model, and the observations on which it is based, have important implications for clinicians and researchers alike.

Specifically, there is now good evidence that BD often begins as major depression in adolescence or early adulthood, and not uncommonly as a nonspecific anxiety disorder earlier in childhood (generalized, panic, phobia, separation, and social, but not obsessive–compulsive disorder or posttraumatic stress disorder, in our sample). The age-adjusted risk of mood disorder more than doubled in our high-risk offspring with a history of childhood anxiety disorder, emphasizing the clinical importance of anxiety in this population. It also clearly illustrates that we cannot rely only on cross-sectional DSM criteria for diagnostic formulation and must take a developmental approach, and, in other areas of medicine, include the familial risk and the clinical course in our assessments and diagnostic formulations—especially in youth early in the course of an evolving major psychiatric illness.

The observation of developmental heterotypy (a disorder predicted by a different [earlier] disorder) has been reported by others,<sup>58</sup> including the Dunedin longitudinal study,<sup>59</sup> in which major psychiatric disorders in young adults were largely predicted by psychiatric disturbance in adolescence, often of a very different nature. Further, genetic studies have demonstrated that childhood anxiety, but not childhood depression, has a shared genetic diathesis with adolescent depression, which itself is continuous with adult mood disorders.<sup>60</sup> Finally, longitudinal studies of people at risk for psychosis have described an early prodrome characterized by nonspecific psychopathology that overlaps with numerous other psychiatric disorders.<sup>1</sup>

Without recognizing that major psychiatric illnesses such as BD and schizophrenia evolve and progress in a series of recognizable clinical stages, the hope of early accurate diagnosis and therefore early effective intervention is lost. It is a point of

interest that most of the affected offspring in our study had been referred to specialized child mental health services early in their evolving clinical course. However, despite multiple generations of affected relatives, including their own parent, none of these symptomatic high-risk offspring were considered as possibly on the trajectory to developing BD. Not uncommonly these symptomatic high-risk youth were treated with play therapy, family therapy, antidepressants, and stimulants at a point in the clinical course where these interventions were either clinically unhelpful or worsened the course of illness.

Addressing this issue, Bauer et al, editors, published a case series (see Duffy<sup>34</sup>) demonstrating that high-risk offspring manifesting moderate-to-severe anxiety and (or) depression did not benefit or were made worse (for example, rapid cycling and switching) by guideline-based treatment, even though these medications were indicated for the presenting DSM diagnosis (moderate-to-severe anxiety, sleep and concentration problems). Other clinical researchers have discussed paradoxical outcomes in symptomatic high-risk subjects treated with stimulants and antidepressants.<sup>61,62</sup> Double-blind randomized trials are needed to determine what interventions (for example, psychotherapeutic, pharmacological, and nutritional) are effective at which critical stages in the early course of BD. Along with determining if these interventions prevent or delay progression of the illness, we need a thorough determination of the risks and benefits of intervening or not at specific stages of illness development. By relying only on the current diagnostic system this research will simply not be possible.

Another clinical concern involves the differentiation of primary mood disorders (melancholic recurrent depression and BD) from other problems featuring prominent mood symptoms, to provide effective treatment and improve outcomes for all of these patients. This difference is important because there are effective treatments for correctly identified patients with melancholic depression and BD,<sup>8,47</sup> which can normalize an otherwise markedly increased mortality rate in untreated patients.<sup>63</sup> Further, there is accruing evidence from basic neuroscience, as well as from clinical and high-risk studies,<sup>64,65</sup> that the prevention of recurrences, psychosis, and complications such as SUDs and (or) associated medical problems, is important to preserving the quality of remission, preventing cognitive deficits, and the associated anatomical changes that may be related to treatment refractoriness. Conversely, lithium will not help psychologically based mood dysregulation or neurotic depression<sup>47</sup> and nonmelancholic depression will respond as well or better to psychotherapeutic intervention rather than to pharmacotherapy.<sup>66</sup>

## Organization of Service Implications

As a consequence of the above new findings, one could offer a set of recommendations for an effective evidence-based early identification specialty service for mood disorders

within child and youth mental health programs. That is, major mood disorders (melancholia and bipolar spectrum disorders) are severe, often lethal brain diseases that have a genetic basis and typically onset in adolescence or early adulthood. To improve early detection, we should aim to identify children at familial risk and monitor them annually in a specialty psychiatric program through the entire risk period from adolescence to early adulthood. Any symptomatic high-risk offspring should be offered a timely, comprehensive psychiatric assessment from a psychiatrist skilled in early detection. We, in child and adolescent psychiatry, should be collaborating much more closely with our colleagues who work with adults to identify high-risk families and with other child mental health services to expedite referrals of high-risk offspring (those with a confirmed familial risk) to these specialty high-risk psychiatric programs. Continuity of surveillance across the entire risk period is critical, as adolescence and early adulthood represents the peak risk time for onset and recurrence of major mood episodes, yet the population aged 15 to 24 years are the least well-served sector.<sup>67,68</sup>

In the current organization, symptomatic children and adolescents at high risk for major mood disorders are not differentiated from patients suffering from various other problems that feature prominent mood symptoms, including: mood dysregulation, reactive depression, and (or) behavioural disorders of a psychological or sociological origin. Further, in child mental health programs, psychiatry often has an ill-defined role. From a clinical, academic, and administrative perspective, the status quo is not only suboptimal for patient care but also an inefficient use of expertise and funding. A better model perhaps would be one in which child and adolescent psychiatrists focus on developing programs to support the early identification and treatment of evolving major psychiatric disorders, while the broader child mental health programs focus on primary mental health. The latter would include a focus on mental health promotion and addressing modifiable risk factors (family dysfunction, child abuse and [or] neglect, bullying, and nutrition and general health) in youth, not at specific genetic risk of a major psychiatric illness, and working in close collaboration with family medicine, schools, and social services, while establishing and maintaining direct consultation links with psychiatry.

This is not to say that psychiatric patients do not benefit from evidence-based psychosocial interventions or that psychosocial risk factors do not play an important role in the clinical course of major psychiatric disorders—they certainly do! However, for best outcomes in patients manifesting major psychiatric disorders, psychosocial support should be delivered in the context of a specialty psychiatric program that focuses on evidence-based treatment of the underlying brain disease, while taking into account the relevant psychosocial context of the patient and family and monitoring the overall medical health of the patient.<sup>69,70</sup>

Around the world, there have been numerous clinical and research subspecialty programs organized to identify young

people at risk for and (or) in the early stages of evolving psychosis. Longitudinal research has demonstrated that ultra-high-risk patients identified by genetic predisposition and clinical indicators, have a very high conversion rate to frank psychosis during a relatively short period of follow-up.<sup>1,71</sup> Further, transition rates to full-blown psychosis have been significantly reduced by early intervention, even with relatively noninvasive treatments including essential fatty acids and psychosocial interventions, in addition to more traditional second-generation antipsychotics.<sup>72,73</sup>

## Research Implications

If it is the case that, in people at genetic risk for BD, the early signs and symptoms of illness manifests as nonspecific sleep and anxiety disorders, and in some neurodevelopmental problems, then one question is why? These so-called stages are not specific to BD and the same can be said for the early stages of many other major psychiatric illnesses, including, recurrent major depression, SUDs, and psychotic disorders. However, the specific familial risk narrows the trajectory for individual patients. Could it be that the developing brain only has limited ways of manifesting an underlying disturbance, such that different pathophysiological processes look at the clinical level the same early in development? Do certain major psychiatric disorders share, to a degree, underlying pathophysiological processes modified by specific disease genes, epigenetic effects, or other gene–environment interactions during development? What are the inherited abnormalities and pathological correlates of evolving BD, and would this knowledge lead to a testable model for understanding illness progression? Is early intervention in BDs justified? Would noninvasive treatments (psychotherapy and essential fatty acids) be effective in the early stages and prevent progression to end-stage major depressive and manic episodes? These are a few of the main research questions stemming from work completed to date; questions that can only be addressed in future prospective studies of carefully selected and clinically assessed high-risk children.

## Closing Remarks

Longitudinal studies of children at familial risk for BD have shed light on seemingly contradictory and hard to reconcile findings that have emerged from earlier cross-sectional high-risk studies and studies of pediatric clinical populations. Specifically, high-risk longitudinal studies have highlighted the role of heterogeneity of mood disorders, and emphasized the importance of a developmental approach and of incorporating the family history in early diagnostic and treatment decisions. Further, high-risk studies have underscored that substantial morbidity early in the course of BD relates to the depressive polarity of the illness (minor depression, and adjustment with depressed and anxious mood and major depressive episodes) and have provided evidence of the evolution of psychopathology through a series of identifiable clinical stages. Future studies, refining the characterization of the early stages of BD and identifying inherited

neurobiological vulnerabilities, intermediate pathways, and pathophysiological correlates of illness progression are of critical importance. In the meantime, we have sufficient evidence to make fundamental changes to the way in which we organize psychiatric care for children and adolescents at high risk of developing major mood disorders. That is, appropriate psychiatric care should be provided in a specialized setting with continuity of surveillance into the adult years. In this regard, specialty clinical and research programs targeting prepsychotic youth can stand as an important testament to the effectiveness and importance of this approach.

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## Résumé : Les débuts de l'histoire naturelle du trouble bipolaire : qu'avons-nous appris de la recherche longitudinale chez les jeunes à risque élevé?

La recherche longitudinale chez les jeunes à risque élevé a produit des données probantes convergentes révélant que les troubles de l'humeur et psychotiques majeurs se développent souvent à partir d'antécédents non spécifiques chez les personnes prédisposées, au fil du temps et du développement. Par exemple, le trouble bipolaire (TB) semble évoluer à partir d'antécédents non spécifiques de l'enfance, notamment l'anxiété et des problèmes de sommeil, suivis d'un ajustement et de perturbations mineures de l'humeur au début de l'adolescence, qui aboutissent à des épisodes majeurs de l'humeur en fin d'adolescence et au début de l'âge adulte. Par conséquent, il faut repenser l'approche diagnostique actuelle, transversale et basée sur les symptômes : elle ne tient compte ni du risque familial, ni du cours clinique longitudinal, ce qui fait que les premières phases de la maladie ne sont pas reconnues appartenir à la phase finale du trouble. De nouvelles données probantes identifient des phases cliniques dans le développement du TB ont un potentiel formidable pour l'identification précoce, le développement de traitements spécifiques à chaque phase, et l'évolution de notre compréhension de la pathophysiologie associée à l'apparition et à la progression de la maladie. Le modèle de starification clinique comporte aussi des implications directes pour l'organisation optimale des services cliniques pour les jeunes à risque élevé. Spécifiquement, il faut des programmes psychiatriques spécialisés qui abolissent les barrières institutionnelles traditionnelles pour offrir une surveillance et une évaluation psychiatrique complète en temps opportun durant toute la période de risque, de l'enfance au début de l'âge adulte. À cet égard, le développement de programmes psychiatriques spécialisés visant à identifier les jeunes qui sont aux phases précoces d'une psychose évolutive est considérablement en avance sur celui de services pour les jeunes aux phases précoces de troubles de l'humeur majeurs évolutifs.