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REVIEW ARTICLE

# Challenges and developments in research of the early stages of bipolar disorder

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Recently, attention in the field of bipolar disorder (BD) has focused on prevention, including early detection and intervention, as these strategies have the potential to delay, lessen the severity, or even prevent full-blown episodes of BD. Although knowledge of the neurobiology of BD has advanced substantially in the last two decades, most research was conducted with chronic patients. The objective of this paper is to comprehensively review the literature regarding the early stages of BD, to explore recent discoveries on the neurobiology of these stages, and to discuss implications for research and clinical care. The following databases were searched: PubMed, PsycINFO, Cochrane Library, and SciELO. Articles published in English from inception to December 2015 were retrieved. Several research approaches were used, including examination of offspring studies, retrospective studies, prospective studies of clinical high-risk populations, and exploration of the progression after the first manic episode. Investigations with neuroimaging, cognition assessments, and biomarkers provide promising (although not definitive) evidence of alterations in the neural substrate during the at-risk stage. Research on BD should be expanded to encompass at-risk states and aligned with recent methodological progress in neuroscience.

**Keywords:** Bipolar disorder; mania; early stages; prodromal; at-risk; offspring

## Introduction

Bipolar disorder (BD) is a chronic, relapsing, and potentially progressive disorder.[1-3] Recently, a focus on prevention, including early detection and intervention, has begun to attract increasing attention, as such strategies have the potential to delay, lessen the severity, prevent progression, or even prevent full-blown BD.[4,5] The notion that BD is a condition that follows a reasonable, predictable course across stages was a key aspect in developing proposals for prevention and early intervention.[6] Indeed, there are consistent data suggesting that, at least for a large subgroup of patients, BD actually follows a progressive course, which can be observed both in clinical outcomes (such as functional impairment) and in neurobiological findings (such as structural brain damage).[7,8]

According to these models, the disorder starts during the "at-risk period" and progresses from the first mood episode through to late-stage disease, where symptoms are more chronic, pervasive, and treatment-resistant, and putatively caused by brain changes related to the action of neurotoxic mediators and reduction of neurotrophic and neuroprotective support.[2,9] The progression of BD results in increasing severity of clinical symptoms, cognitive impairment, and functional deterioration, demanding more complex and expensive treatment alternatives.[2] From this perspective, prevention of BD progression is paramount to reducing the major economic, psychosocial, and functional impact of this disorder on patients, families, and societies.

Knowledge of the neurobiology of BD has advanced substantially in the last two decades. Nevertheless, most studies have been conducted with chronic (i.e., late-stage) patients.[10] Biomarkers seem to play an important role in evaluating disease activity and progression associated with different mood states (mood biomarkers), as well as to identify specific characteristics of the disease (trait biomarkers).[11,12] The available evidence indicates that neurotrophins, oxidative stress, and inflammation are linked to the acute and euthymic phases of BD,[13,14] and indicate the presence of systemic toxicity.[15]

The use of clinical staging models is emerging as a novel and useful paradigm to inform diagnosis and

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treatment of BD.[16-18] Staging models and the concept of neuroprogression represent significant advances in the field and provide a new scientific base for early intervention.[7,19-21] The term neuroprogression has been increasingly used to define the pathological reorganization of the central nervous system (CNS) that occurs over the course of severe mental disorders.[12] This reorganization may arise as the result of several "insults," such as inflammation and oxidative stress.[12] To refine clinical staging models and identify novel, specific targets for early intervention, it is essential to understand the pathophysiological processes associated with the clinical stages of illness development.[17,22] Indeed, there is convergent evidence from longitudinal studies to support the hypothesis that BD develops in a series of predictable clinical stages in those at genetic risk.[22,23]

Nevertheless, few studies have approached the early stages of BD, and data on potential neurobiological differences between early- and late-stage BD are scarce.[12] This is a notable contrast to the field of psychosis, in which a large proportion of research resources has been targeted at understanding, recognizing, and managing early-stage disease.[24-27]

The objective of this article was to provide a comprehensive review of the literature on neurobiology of the early stages of BD, with a special focus on the late prodromal stage and the period surrounding the first episode of mania. We also aimed to discuss the implications of emerging research findings in this field for investigation and clinical care.

## Search strategy

A comprehensive literature search of computerized databases (PubMed, PsycINFO, Cochrane Library, and SciELO) was performed using the following terms: "bipolar disorder," "mania," "manic-depressive illness" cross-referenced with "prevention," "early detection," "early intervention," "bipolar at risk," "prodromal," "preclinical," "at risk mental states," "clinical high risk," "ultra-high risk," "first episode of mania," "biomarkers," "brain-derived neurotrophic factor," "inflammation," "cytokines," "oxidative stress." Articles published from inception to December 2015 were retrieved. Selection of articles for inclusion in the review was based primarily on the information available in the study abstracts. The reference lists of the selected articles were also hand-searched for additional, potentially relevant citations. The exclusion criteria were articles written in languages other than English and studies of juvenile or pediatric BD (as we wished to focus on the adult phenotype of BD).

## Clinical presentation of early stages

The gradual evolution of BD has been well recognized by individuals, their family members, and clinicians. In fact, there are convergent findings in the literature from extensive clinical observations regarding to the period of weeks, months, or even years during which mild, intermittent, and subthreshold mood symptoms are present before the onset of the first mood episode.[28,29] Several studies have recognized mood lability, major depressive episodes, subsyndromal manic symptoms, a diagnosis of a bipolar spectrum disorder (such as cyclothymia or BD not otherwise specified), and mood-congruent psychotic symptoms as precursors of BD.[30-32] On the other hand, in clinical practice, identification of a symptomatic high-risk BD phase is complicated by the complex nature of dimensions of this disorder, by potentially different symptom presentations in children and adolescents,[5,21,33] and by the blurred lines between the prodrome and the disease itself.[34]

Retrospective and prospective studies have revealed a pattern of putative prodromal symptoms, of which mood lability/mood swings/cyclothymic features, depressive mood, racing thoughts, irritability, and physical agitation are most commonly reported.[4,21] Considering that the onset of first manic episode occurs mainly in adolescence and early adulthood, it can be assumed that mild, poorly differentiated, or nonspecific symptoms influence the earliest developmental stages of the individual.[35,36] In fact, retrospective studies have shown that BD patients may report symptoms as early as 2 years of age, even though these manifestations are highly unspecific (such as sleep disorders or excessive crying).[37-39] Over time, with the progression of psychopathology across personal developmental phases (childhood, puberty, adolescence, etc.), there is a trend for symptoms to become more specific and more similar to BD.[40] Accordingly, a 4-year follow-up study found that 38% of children and adolescents initially diagnosed with subsyndromal symptoms of BD (usually cyclothymia and BD not otherwise specified) and 25% of those diagnosed with type II BD were ultimately diagnosed with type I BD during the follow-up period.[41]

## Study designs for the early stages of BD

### *Offspring studies*

BD is a highly heritable disorder, with up to 85% of the variance in risk determined by genetic factors; hence, a positive family history is still the best predictive factor for development of the illness.[18,22,23] However, a family history does not merely predict an increased risk of BD. Meta-analyses have shown that, compared to other children, the offspring of a BD parent (OSBP) have an eight- to tenfold increase in lifetime risk of developing BD, but also a threefold lifetime risk of any severe mental disorder (e.g., psychosis) and one-in-two odds for any mental disorder.[42] Thus, OSBP studies provide a reliable and valid means for identifying a sample of individuals at high risk of developing mental disorders, and can provide information on prodromal signs and symptoms of BD and rates of transition from "at-risk" state to clinical "caseness."[43] Importantly, the study of OSBP is a useful "enrichment" strategy that may help identify the underlying pathophysiology and evolution of clinical stages of BD over time and access factors such as potential interactions between genetic liability, birth weight, and early-life stress.[44,45]

In addition, studies of OSBP can enhance our understanding of the clinical phenotypes of individuals at high

risk of developing BD and demonstrate the heterotypic continuity of problems with a common developmental pattern, involving, e.g., anxiety problems in childhood, a first mood episode in early adolescence, and a (hypo) manic episode in late adolescence or early adulthood.[22,23] Prospective studies have the potential to clarify the illness trajectory by exposing the temporal relationship between childhood difficulties or non-mood problems and later affective pathology or development of BD. Questions as to whether non-mood pathology represents a risk syndrome or earlier manifestation of the disorder or whether it is a concurrent disorder in its own right may be answered by such studies of high-risk children. Furthermore, the longitudinal follow-up of affected and unaffected high-risk siblings from an early age allows exploration of clinical, biological, and environmental factors that may predict which high-risk family members ultimately develop BD.[46]

However, when reviewing the findings on neurobiology and staging that derive from OSBP studies, it is important to consider differences in methodology.[47] There are often differences in the sampling or recruitment strategy employed (clinical/community; offspring of one affected parent/two affected parents), the assessments used (self/observer-rated), and the timeframe of assessment (cross-sectional/longitudinal; retrospective/prospective). The methods employed to recruit families into OSBP studies also vary widely, and include recruitment of families already involved in neurobiological and genetic research projects,[48] recruitment of all or some participants via self-referral and/or advertising campaigns,[49] recruitment from hospital settings and specialized clinics,[50] and from patient advocacy associations.[44] Notably, higher rates of comorbidity are evident in studies that recruit via self-referral and families where the non-proband parent also had a non-affective psychiatric illness. Likewise, the nature of the control group also influences findings. For example, studies which included healthy children as controls demonstrated a major increase in a range of psychopathology in the OSBP, while studies using children of chronically medically ill parents (so-called positive controls) often show high levels of psychopathology in the comparison group as well as in the OSBP group.[51] Finally, the use of pediatric or adult diagnostic criteria to identify BD, and the use of dimensional rather than categorical measures of psychopathology, may influence study findings.[46] These issues are highly relevant to any comparisons of data regarding neurobiology of the stages of BD, as heterogeneity in OSBP clinical phenotypes or illness trajectories may obscure rather than clarify our understanding of clinicopathological boundaries across illness stages.

### *Retrospective designs*

The majority of studies investigating the prodrome of BD have used retrospective designs.[3] These studies support the existence of a prolonged, symptomatic prodrome prior to the first episode of BD.[52] Symptoms reported retrospectively during the prodromal phase include both mood (depressive symptoms, manic symptoms, mood lability, cyclothymia) and non-mood features (such as anxiety, sleep and concentration problems, and energy changes).[53]

Retrospective studies of the BD prodrome have used a variety of methods to assess data from patients and caregivers, thus limiting comparison across studies.[52] Most used either unstructured questionnaires or chart reviews, and failed to assess the onset pattern of the disorder and the symptom severity of the prodromal period, which limits validity.[5] Furthermore, it remains unclear which person (i.e., the patient, a parent, teacher, or peer) is most likely to first notice the prodromal symptoms.[5] Thus, studies that access information regarding prodromal symptoms only from the point of view of patients themselves may be less reliable. Finally, recall bias is another limitation that must be taken into account when analyzing findings on neurobiology derived from retrospective studies.[53]

### *Prospective studies of first-episode mania*

Prospective studies of first-episode mania are crucial to improving our understanding of the development, onset, and progression of BD. This strategy allows us to identify clinical correlates that might characterize patients at risk of poor medium- to long-term outcomes, and avoids the confounding effects of multiple episodes, morbidity, comorbidities, and treatment.[54,55] Additionally, this approach may help optimize treatment planning for the clinical, cognitive, and functional characteristics of patients identified as being at different, distinct stages of the illness.[56]

Different methodologies have been used in first-episode studies, and this must be taken into account when interpreting results from such investigations.[57-59] For instance, there is a lack of homogeneity regarding the definition of first mood episode. Follow-up studies have included patients with different mood states (mania, mixed states, or BD depression); included mixed samples of patients with BD and psychosis; or have defined first-episode onset as the first hospitalization.[57,59] The mean age of the BD sample is another limitation in some studies. In our review of the literature, it is notable that most first-episode BD studies were conducted in adults[60,61] and very few included children or adolescents.[62,63] The nature of the control groups used in these first-episode studies is also a topic of some debate.[59,64] Findings that emerge from studies comparing BD cases with healthy controls or probands to their relatives have shown consistent differences in regard to cognition. However, the magnitude of these differences in cognitive functioning itself differs according to the choice of control group. Overall, when compared to healthy controls, BD cases demonstrate more overt cognitive impairment, whereas smaller differences in cognitive performance have been observed when BD cases are compared to healthy relatives.[59] This may point to methodological issues, or may represent a genuine link between a clinical phenotype and an inherited endophenotype.[65] However, disentangling these issues is complex, as even first-episode studies include many patients on polypharmacotherapy, and the

possible triggering effect of these drugs has not been considered.[57,59]

*Prospective studies of individuals at clinical risk of BD*

Prospective studies of individuals at risk of BD present a potentially reliable and valid approach to understanding the progression of BD psychopathology.[4,66] Many studies use enrichment strategies to enhance the possibility of studying a sample in which a large proportion of subjects experience onset of BD. However, the disadvantage of this approach is that it may limit the universality of findings, due to lack of power or specificity for predicting BD as compared to onset of a range of mental disorders.[53] High-risk prospective studies investigate individuals that are at specific risk of developing BD due to genetic loading or presence of early manifestations of psychiatric symptoms at a subclinical level,[53] in the so-called close-in strategy.[21]

Research into the prodromal phase of BD has led to the assumption that individuals presenting at preclinical stages of BD may be identified. Initially, ultra-high risk (UHR) or bipolar at-risk (BAR) criteria for BD have been proposed, assuming that the initial phases of the disease may present with symptoms that are insufficient in severity, frequency, or duration. These criteria include: (a) subthreshold mania; (b) depression with cyclothymic features; or (c) depression associated with genetic risk for BD.[67] Recently, the BAR criteria were validated in a prospective study of adolescents and young adults. In the BAR group, 14.3% converted to first-episode hypomania/mania (as opposed to none in the control group) at 1-year follow-up, with subthreshold mania having the greatest predictive value.[4] In future, strategies to identify at-risk individuals will be partly dependent on the development of measurement scales with robust psychometric characteristics, such as the recently validated Bipolar Prodrome Symptom Interview and Scale-Prospective.[3]

## Neurobiology of the early stages of BD

*Neuroimaging*

Neuroimaging investigations of structural and functional brain abnormalities in individuals at genetic risk of BD offer several advantages: identifying brain abnormalities that potentially predate the onset of BD and are not confounded by factors such as illness duration or medication; identifying brain abnormalities that may confer risk for or protect against BD, to inform evaluation of risk of BD development and subsequent therapeutic intervention; and improving understanding of the developmental course of BD.[68] Furthermore, neuroimaging abnormalities found in individuals at high genetic risk may underlie the modest neurocognitive impairments (namely, executive function and working memory deficits) observed in relatives of patients with BD.[68]

A number of imaging studies in individuals at genetic risk for BD are available, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and structural magnetic resonance imaging (MRI) studies, which investigate grey- or white-matter volumes. Despite this large volume of published research, findings have been inconsistent, and no reliable structural or functional markers of genetic liability to BD have been identified.[68] An advantage of neuroimaging studies of young patients with BD is that they may help clarify neurodevelopmental aspects of the illness and identify biomarkers of disease onset and progression.[68] Brain imaging techniques such as MRI, PET, and DTI are being used increasingly for direct quantification of neural system abnormalities associated with BD and high risk of BD.[68]

Neuroimaging techniques are also some of the most powerful tools available for identification of endophenotypes. Identifying endophenotypic markers would help to confirm a likely diagnosis of BD; could allow clinicians and researchers to discriminate BD depression from unipolar depression; and, potentially, enable identification of at-risk individuals who will subsequently develop the illness, thus facilitating early intervention.[68,69] Relevant findings in BD to date have centered on functional and structural neuroimaging studies, underlying core domains of the pathology in children with BD and those at high risk.[68,69] As new protocols, techniques, and technologies emerge, there is the possibility of addressing important clinical questions, including the identification of treatment-relevant endophenotypes to create treatment response groupings to meet the long-term goal of rational treatment advances for BD.[68,69]

A recent meta-analysis showed that grey-matter loss may be a state-related factor for BD, suggesting that structural imaging may be a useful biomarker to distinguish individuals who will transition to BD from those who will not.[69] However, prospective studies of grey-matter volume in high-risk individuals are needed to evaluate this finding.[69] The same meta-analysis found that hyperactivation in the frontal and insular cortex is the neural substrate for the executive function impairments seen in high-risk individuals and patients with BD.[69] The similarity between these findings in high-risk individuals and previous findings in patients with BD suggests that hyperactivation in these regions is a good candidate trait endophenotype for BD.[69] However, further work is needed to determine how this relates to the affective disturbances and other clinical features that develop with onset of BD.[69]

To date, most studies of white-matter changes in BD have been conducted in older subjects and those with well-established disorders.[70] A recent study reported significant changes in major white-matter tracts in a large cohort of young patients in the early stages of BD.[70] Specifically, this study provided evidence of microstructural white-matter changes within the corpus callosum early in the course of illness.[70] The nature of these changes suggests an association with abnormalities in axon myelination.[70] Collectively, these results are consistent with the notion that BD is associated with discernable abnormalities in white-matter integrity, and that this is driven predominantly by the BD I phenotype.[70]

Another recent study that assessed white-matter microstructure and grey-matter volumes in a community

sample of adolescents with BD found widespread alterations in white matter involving a number of tracts that continue to mature during adolescence.[71] In addition, the authors observed that BD in adolescents is associated with structural connectivity alterations likely to affect the development of white-matter bundles and connected grey-matter areas involved in emotion regulation.[71]

Since patients with BD have been reported to show hippocampal abnormalities, a recent systematic review of 25 studies analyzed hippocampal volume.[72] The results were consistent with decrease in hippocampal volume in four of 18 studies using adult samples and two of three samples using adolescents. Four studies revealed localized hippocampal deficits.[72] Meta-analysis revealed a significant but small effect with lower hippocampal volumes when comparing all BD patients vs. controls.[72] Lithium treatment was associated with larger hippocampal volumes across studies. Three functional studies were included and yielded contradictory evidence; the authors concluded that BD seems to feature a minor reduction in hippocampal volume, which may be more pronounced in early-onset BD and counteracted by a neuroprotective effect of lithium treatment.[72] However, how these structural abnormalities relate to functional deficits is largely unclear.[72] Given the paucity of functional neuroimaging studies and lack of congruence in their results, further investigation of hippocampal function in BD is recommended.[72]

The Systematic Treatment Optimization Program for Early Mania (STOP-BD) study used single-voxel proton MRS to assess hippocampal neurometabolite levels in patients with BD recruited within 3 months of recovery from first manic episode. In this study, glutamate plus glutamine (Glx) and N-acetyl aspartate levels were no different between BD patients and matched healthy subjects at baseline, and levels did not change differentially during the 1-year follow-up period in BD patients compared with controls. This suggests that patients in the early stage of BD did not experience alterations in hippocampal neurochemistry, and supports the importance of early interventions to arrest illness progression in BD.[73]

In summary, translating knowledge of the neuroanatomy of BD into a diagnostic tool or test paradigm will require identifying the neural signature of predisposition for BD (potential cause) and separating it from the effects of long-standing illness and treatment (possible consequence of the disease process).[74] Finally, structural neuroimaging studies focusing on volume could aid in the identification of individuals at risk of BD even before any behavioral manifestation, and further research into associations among genetic risk, illness burden, lithium treatment, and brain structure in BD could be useful.[74]

### *Neurocognition*

There is mounting evidence that individuals with BD experience neurocognitive deficits even in remission periods.[65,75,76] This may be explained, in part, by the progressive course of illness involving relapses with increasing severity of residual symptoms, comorbidity with other psychiatric and medical conditions, and adverse effects of treatment. However, whether these cognitive deficits occur early in the course of BD or predate the onset of the diagnosable mood disorder is not yet clear.

Distinct methodologies have been used to investigate cognitive function in the premorbid stage of BD, both in general population studies (e.g., conscripts to national service or community-based cohorts) and in clinical high-risk or genetic studies of BD.[59,66] For instance, three "conscript" studies included young adults recruited from the armed forces and followed these individuals prospectively over long periods, but provided inconsistent or inconclusive findings.[77-79] Zammit et al.[79] suggested that individuals who developed BD had cognitive performance comparable to that of healthy controls, while Tiihonen et al.[78] showed that individuals who developed BD had superior performance in arithmetic but poorer visuospatial reasoning than healthy controls.

Another way to investigate neurocognitive functioning is to examine individuals at high risk of mood disorders/psychoses who are prospectively diagnosed as having BD. Using this methodology, Meyer et al. found comparable premorbid intelligence quotient (IQ) values between BD offspring and controls, while poorer executive function was observed among subjects who developed BD.[80] In contrast, Olveta et al., in a follow-up study involving adolescents at high risk of developing psychoses, reported no differences in premorbid IQ or global neurocognitive scores between subjects who developed BD and those who did not transition to psychiatric illness.[81] More recently, Ratheesh et al.[66] investigated young people at UHR of psychoses during the prodromal phase of the illness and followed them prospectively for approximately 8 years. Most cognitive measures did not differ between subjects who developed BD and those who did not transition to psychoses or BD.[82] Subjects also showed appropriate cognitive function (e.g., visual information processing) before the onset of BD.

Assessment of cognitive functioning from the first episode of mania is important to better understand whether cognitive deficits are already present at the early stages of illness or are progressive. To date, we have identified three meta-analyses that examined cognitive functioning in patients in first-episode mania.[57-59] Lee et al.[59] included 12 studies of cognition involving young adults (mean age, 28.2 years) with first-episode mania or mixed states, depression, or psychoses. Greater cognitive impairment (with a modest effect size) was found in patients compared to controls across eight domains, except for visual learning and memory. These cognitive dysfunctions were independent of current mood state, with the exception of response inhibition, which was found only in symptomatic patients. Similarly, Daglas et al.[57] investigated the cognitive profiles of adults and adolescents during the acute phase of mania and the period following symptomatic recovery. The findings of this meta-analysis were inconclusive, although individual studies have previously reported cognitive dysfunctions in specific domains during the asymptomatic period. More recently, Trota et al.[58] reported data from a meta-analysis that compared global intellectual functioning measured

before or following illness onset in psychiatric patients and controls. Interestingly, individuals with BD demonstrated poorer premorbid intellectual function than controls when function was measured retrospectively, but not when measured prospectively; BD cases also exhibited moderate cognitive impairment after onset of illness. A 1-year follow-up study in first-episode BD showed that cases differed from controls with regard to specific cognitive domains, such as processing speed, executive function, verbal and nonverbal memory, and working memory. Moreover, cognitive improvement (processing speed and executive function) was observed in patients after 1 year of follow-up, particularly in those without a history of substance abuse and who had discontinued antipsychotic treatment.[55]

Comparing results from studies of first-episode mania to those of BD cases with multiple episodes, Lopez-Jaramillo et al.[60] observed worse cognitive performance (attention, processing speed, and executive function) in euthymic patients who had experienced at least three manic episodes as compared with patients who had only one prior BD episode. Other researchers have also demonstrated that patients who have had multiple episodes are more likely to present with deficits in executive function and verbal memory than those at early stages of BD.[62,83] Furthermore, cognitive deficits may also limit long-term psychosocial functioning, which means that patients with greater cognitive impairment are more likely to experience poorer outcomes. In this regard, we previously reported progressive functional decline from the early through late stages of BD.[84] These findings are consistent with previous studies indicating an association between cognitive deficit and BD severity.[62,85] The number of manic episodes is strongly associated with cognitive impairment,[60,86] while other clinical features, such as subsyndromal depressive symptoms,[75] illness duration,[87] psychotic symptoms,[87] number of hospitalizations,[85] psychiatric comorbidities,[55,87] medications,[6,55] and adherence,[87] have also been shown to correlate significantly with cognitive impairment.

In short, early intervention could play a crucial role in preventing illness progression (and any associated cognitive/functional decline) in BD. Primary prevention could be used to treat individuals at UHR of developing psychiatric disorders, as well as patients in stage I (more specific but still subsyndromal symptoms).[88] There is evidence supporting the neuroprotective benefits of early interventions for stage I patients, with the possibility of preserving cognitive and psychosocial functioning.[76,89,90]

### *Biomarkers*

As several different sets of symptoms and risk factors might be present prior to full-blown BD, a cluster of features including trait factors (such as genetic risk and personality traits) and state-related factors (such as subthreshold symptoms) might best capture the "at-risk" state for BD.[4] Moreover, correlating these symptoms with prodromal biomarkers offers an exciting juncture whereby targeted interventions could be opportunistically employed to prevent neurodegenerative changes from accruing as the disease progresses.[11,91] Nevertheless, empirical data supporting the use of biomarkers for outcome prediction in prodromal stages are limited.[92] One of the first studies, conducted by Padmos et al.,[93] identified a discriminating and coherent expression of 19 pro-inflammatory genes transcription in monocytes of patients with BD and in the offspring of BD parents. These results were in line with the work of Mesman et al.,[23] who conducted a longitudinal follow-up study and found that, during adolescence, offspring of BD parents demonstrated increased inflammatory gene expression in monocytes, high serum levels of pentraxin 3 (PTX3; a regulator of inflammatory response), but normal levels of the chemokine CCL2,[23] as well as decreased levels of brain-derived neurotrophic factor (BDNF). During young adulthood, monocyte activation remained, although to a lesser degree; serum PTX3 levels remained high; and signs of monocyte migration became apparent through increased CCL2 levels. In adulthood, circulating monocytes had lost their activation state, but CCL2 levels remained increased, and both BDNF and S100B were increased. These abnormalities were independent of psychopathology state at all stages.

The identification of biological markers associated with clinical symptoms of imminent mania onset (in clinical high-risk individuals) might help increase the odds of early detection of BD and allow selection of subgroups for implementation of prevention strategies.[5] To date, only preliminary data about biomarkers in at-risk states are available. These indicate that individuals at high risk of developing BD may have higher levels of lipid peroxidation as compared with healthy controls and lower levels compared with young people with syndromal BD.[94] In addition, small-scale studies have suggested that changes in sleep, circadian rhythm, and social rhythm regularity are altered in at-risk youths compared with age- and gender-matched healthy controls.[95-97] The predictive power of these biomarkers for transition to BD at follow-up is unknown.[9]

## Conclusions

This review highlights not only the emerging evidence but also the critical gaps in our knowledge about the early stages of BD. One of these gaps is the urgent need to develop consensus-based criteria to define at-risk or clinical high-risk states. It is also important to harmonize recruitment criteria for offspring studies or, at least, to mandate reporting of the sampling strategy employed, thus allowing readers to compare the influence of recruitment on outcomes. The current use of disparate criteria makes if difficult to compare findings across studies and to generalize findings to other locations or to clinical practice. Incorporation of biomarkers into research on the early stages of BD is also a necessity, as clinical phenotypes alone are highly unlikely to have predictive validity for BD onset. However, research on biomarkers in psychiatry in general is still in its infancy and beset by methodological issues, including reproducibility, replication, validity, and integration concerns.[92,98,99]

Another challenge in predicting outcomes is the need to develop and apply big-data bioinformatics platforms to

analyze and integrate the volume of data available from large samples, multiple samples, and international multicenter studies.[100] Bioinformatics tools allied to system biology paradigms may support more robust discoveries on the early stages of BD than any single approach on its own.[101]

Despite gaps in our knowledge, it is still vital to raise awareness among mental health professionals of the need for more timely and accurate diagnosis of BD, so as to enable recognition of the putative prodromes of BD as early as possible and, consequently, to minimize the use of antidepressant or psychostimulant monotherapies in at-risk individuals. This has been an important first step in promoting the philosophy of early intervention in psychosis, and is equally important for the field of mood disorders.[21,30]

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