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Early Intervention in Bipolar Disorder

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Bipolar disorder is a recurrent disorder that affects more than 1% of the world population and usually has its onset during youth. Its chronic course is associated with high rates of morbidity and mortality, making bipolar disorder one of the main causes of disability among young and working-age people. The implementation of early intervention strategies may help to change the outcome of the illness and avert potentially irreversible harm to patients with bipolar disorder, as early phases may be more responsive to treatment and may need less aggressive therapies. Early intervention in bipolar disorder is gaining momentum. Current evidence emerging from longitudinal studies indicates that parental early-onset bipolar disorder is the most consistent risk factor for bipolar disorder. Longitudinal studies also indicate that a full-blown manic episode is often preceded by a variety of prodromal symptoms, particularly subsyndromal manic symptoms, therefore supporting the existence of an at-risk state in bipolar disorder that could be targeted through early intervention. There are also identifiable risk factors that influence the course of bipolar disorder, some of them potentially modifiable. Valid biomarkers or diagnosis tools to help clinicians identify individuals at high risk of conversion to bipolar disorder are still lacking, although there are some promising early results. Pending more solid evidence on the best treatment strategy in early phases of bipolar disorder, physicians should carefully weigh the risks and benefits of each intervention. Further studies will provide the evidence needed to finish shaping the concept of early intervention.

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Remembering Our Past As We Envision Our Future

April 1925: Interpretations of Manic-Depressive Phases

Earl Bond and G.E. Partridge reviewed a number of patients with manic-depressive illness in search of a unifying endo-psychic conflict. They concluded that understanding either phase of illness was "elusive" and "tantalizing beyond reach."

(Am J Psychiatry 1925: 81: 643–662)

William J. Mayo (1861–1939) stated that "the aim of medicine is to prevent disease and prolong life; the ideal of medicine is to eliminate the need of a physician" (1). Hence, physicians have been trying for almost a century to find early interventions that would prevent the onset of diseases, or at least change their course. Big steps have been made in several fields of medicine, such as cardiology and oncology. When it comes to psychiatry, although there is ground for optimism, there is still a long way to go (2).

Difficulties concerning primary prevention and intervention in psychiatry arise mainly from the absence of a clear etiology. Consequently, psychiatry has focused more on tertiary prevention, that is, in the use of therapies aiming to minimize the consequences of clinically established disease rather than to prevent its occurrence (3). However, considering the high prevalence of mental illnesses, their significant contribution to global disease burden among young people, and their considerable impact on public health, the implementation of early interventions in psychiatry should be considered a major priority.

To achieve this goal, and since early intervention focuses on known risk factors and early signs of the illness, there is a growing interest in understanding the early course of psychiatric conditions. For bipolar disorder, until recently most information regarding early manifestations came from retrospective and cross-sectional studies, which have a high risk of recall bias and do not allow assessment of temporality. Still, current evidence suggests that bipolar disorder has a progressive nature (4–6), therefore supporting the existence of milder phases of the condition prior to the classic presentation of the illness. This progressive nature makes bipolar disorder an ideal candidate for early intervention strategies, especially considering that 50%−70% of people with bipolar disorder usually start to manifest mood symptoms before age 21 (7–12). This highlights the need for early interventions to prevent or at least delay the onset of the full syndromal illness during childhood, which is crucial to avoid impacts on normal developmental tasks and psychosocial or neurobiological deterioration (13) and to prevent future complications, such as the development

of psychiatric comorbidities, impaired functioning, or premature death by suicide (14).

Noting that *The American Journal of Psychiatry* is commemorating its 175th year of publication, we see early intervention in bipolar disorder as one of the cutting-edge topics in psychiatry. Although there are limited data based on this concept arising from the area of psychoses, we believe that ongoing and forthcoming research in this field is going to have a long-lasting impact on the field as mental health care increasingly turns its focus to prevention (15). In fact, more than 20 years ago, *The American Journal of Psychiatry* published one of the first articles discussing the role of prodromes and precursors in major depression (16); 10 years later the journal published the first paper proposing early intervention to prevent substance abuse in first-episode bipolar disorder (17) and a landmark trial indicating that first-episode psychosis could be treated with lower dosages of antipsychotics than are used in multiple-episode psychoses (18). Hence, in this review we will focus on the results obtained in longitudinal studies assessing variables considered as predictors of conversion to bipolar disorder or of illness course, conducted in offspring at high familial risk for bipolar disorder, community cohorts, and pediatric populations with diagnoses of bipolar disorder. Finally, the available psychological and pharmacological intervention data in the early stages of bipolar disorder will be covered, as well as the point of view of the authors on future directions of the research on the issue.

IDENTIFYING RISK FACTORS AND PRODROMAL SYMPTOMS AS PREDICTORS OF BIPOLAR DISORDER ONSET AND COURSE

The identification of risk factors or prodromal symptoms defining an at-risk stage has important treatment implications, as early stages are anticipated to be likely to be more responsive to treatment and therefore may need less complex interventions (19, 20). Moreover, psychiatric treatments likely have a more beneficial impact when applied at an earlier stage of the disease (21). A key issue is that the at-risk state in most disorders, including bipolar disorder, is pleomorphic and nonspecific and has the potential to evolve into diverse formed phenotypes or no disorder.

Environmental Risk Factors

Although bipolar disorder has a high genetic loading (22), it is considered a multifactorial disease that is influenced by environmental factors (23), some of which might be used as targets of early intervention strategies since they can be potentially modified (24). Life events have been proposed as triggers of future bipolar disorder (25), but results are controversial. While some studies (26, 27) found a positive association between mean life events and risk of mood disorder, Wals and colleagues (28) found that stressful life events were not related to the onset of mood episodes after adjustment for prior anxious or depressive symptoms. Considering the impact of life events in illness trajectory, lifetime sexual abuse seems to be related to a worse course of bipolar disorder (29–32). Recent public outrage at institutional childhood sexual abuse and campaigns to address this in many countries are an exemplar of a policy approach that may have an impact on a critical risk (33). Antidepressant use in depressed youths also may be a risk factor (34), as antidepressants might induce (hypo)manic symptoms (35).

Substance misuse is a prevalent condition in mood disorders that worsens illness prognosis (36). Moreover, its presence has been related to an increased risk of bipolar disorder at follow-up in patients seeking help for depression, anxiety, or substance use disorder (37). Although some studies have found a lower prevalence of substance use disorder in patients with a first mania episode compared with multiple-episode patients (38–40), this finding suggests that primary prevention of a secondary condition, in this case substance abuse in patients with bipolar disorder, needs to be considered (40). Substance use disorder can be predicted by lifetime alcohol experimentation, lifetime oppositional defiant disorder and panic disorder, family history of substance use disorder, or low family cohesiveness (39); these risk factors show a compounding effect. Presence of mixed features also appears to increase the risk of developing substance use disorder (17). Smoking may be associated with an increased risk of psychiatric disorders from depression to schizophrenia (41). Of concern, even maternal smoking may increase risk in offspring (42, 43).

Biological Risk Factors

Family history of bipolar disorder is one of the more solid risk factors for bipolar disorder (44) and is a primary threshold from universal to indicated prevention strategies. Longitudinal studies conducted in bipolar offspring found that age at onset and mood disorder subtype of the probands influence the heritability and course of bipolar disorder (38, 45, 46). For instance, these studies showed that offspring of early-onset bipolar disorder probands were at an increased risk for any bipolar disorder (45, 46) and that lithium nonresponsiveness in parents was related to a poorer premorbid functioning, a more chronic course, and a higher prevalence of psychotic disorders in their offspring (38).

Neurodevelopmental factors are being studied as potential early markers of specific mental illness. A prebirth cohort study found that child developmental delay assessed with the Denver Developmental Screening Test, which measures fine and gross motor skills, language, and personal–social development, was a predictor of later mania but not of depression or psychosis (47). In the same study, premorbid cognitive ability predicted only psychosis (47). However, there are data indicating that children with the highest academic attainment may be at greatest risk of bipolar disorder, while those with the weakest grades were at moderately increased risk (48) (Table 1).

Prodromal Symptoms

Results from longitudinal studies indicate that bipolar offspring are at a higher risk of developing bipolar disorder than the general population (46, 49–51), but they are equally at risk of developing other psychopathology, such as major depressive

TABLE 1. Main Preliminary Findings on Bipolar and Psychosis Prodromal Stage

Characteristic	Bipolar Disorder Prodromal Stage	Psychosis Prodromal Stage (145, 157)
Main risk factor	Family history of early-onset bipolar disorder	Family history of psychosis
Early symptoms	Subjective sleep disturbances, anxiety, depression	Attention problems, depression, anxiety, avolition, social difficulties, disorganization, sleep disturbances
Proximal[a] symptoms	Subthreshold (hypo)manic symptoms	Subthreshold psychotic symptoms
Neurodevelopmental profile	Superior or low premorbid cognitive functioning	Verbal memory and processing speed deficits

[a] Proximal symptoms are those that appear closer to conversion to full symptomatic episode.

disorder, anxiety disorders, or psychotic disorders (28, 38, 44, 45, 52–54) (Table 2). Similarly, adolescents from community cohort studies who developed bipolar disorder also exhibited significantly high rates of comorbid anxiety disorders and disruptive behavior disorders (55).

As there is strong evidence that the index (hypo)manic episode in both bipolar offspring and community cohorts is frequently preceded by other affective or nonaffective symptoms (38, 49, 52, 55), longitudinal studies have tried to disentangle whether any of these conditions can be considered as early symptoms of bipolar disorder and help to predict future bipolar disorder onset. For instance, in the Dutch bipolar offspring cohort, 88% of the offspring who developed a bipolar spectrum disorder initially presented with a depressive episode, with an average time to bipolar conversion of 5.1 years (52) (Table 2). Subjective sleep problems also may be related to the development of bipolar disorder (56) (Table 2), but more evidence is needed before any firm conclusions can be drawn. Childhood anxiety disorder has been described as a prodromal symptom of major mood disorders, but it seems more related to unipolar depression than to bipolar disorder (44, 54). Anxiety disorders, in turn, seem to be predicted by the temperamental traits of shyness and emotionality (54) (Table 2). In contrast, subthreshold (hypo)manic symptoms have emerged as a key predictor of the development of (hypo)mania in community (37, 57, 58), high-risk (59), and bipolar offspring (45, 49, 50, 60, 61) cohorts (Table 2), even after adjusting for risk factors associated with psychopathology, such as parental psychiatric morbidity (49, 58). Moreover, greater intensity of hypomanic symptoms or earlier age at onset is associated with an increased risk of progressing to bipolar I or II disorder among children and adolescents initially meeting operationalized criteria for bipolar disorder not otherwise specified (62, 63).

Some studies have focused on the predictive value of several dimensional factors and not only in categorical predictors (45, 50, 61). Data emerging from the Pittsburg Bipolar Offspring youth cohort (45) show that offspring of parents with bipolar disorder with significant symptoms of anxiety/depression, affective lability, and subsyndromal manic symptoms were at increased risk of developing bipolar spectrum disorders. While affective lability and anxiety/depression were elevated throughout follow-up in those who later developed bipolar disorder, manic symptoms increased up to the point of conversion. Offspring with all the above risk factors, and particularly those with parents with early-onset bipolar disorder, had a 49% risk of developing bipolar disorder. Similarly, in an Amish cohort of bipolar offspring (50), converters to bipolar disorder showed a higher prevalence of sensitivity, hyperalertness, anxiety, and somatic complaints during the preschool period and more mood and energy fluctuations, tearfulness, sleep disturbances, and fearfulness during school years. However, a meta-analysis reporting data on prodromal symptoms in pediatric and adult samples with bipolar disorder pointed out that even if there are some highly reported prodromal symptoms, the prodromal stage tends to differ between individuals (64).

As bipolar disorder usually first presents with a depressive episode (65), longitudinal studies have assessed the presence of prodromal symptoms of conversion from unipolar depression to bipolar disorder (Figure 1). The main replicated finding is the relationship between diagnosis of psychotic depression and switching to (hypo)mania (66–69). A recent meta-analysis identified a family history of bipolar disorder, an earlier age at depression onset, and the presence of psychotic symptoms as most robustly predicting conversion from depression to bipolar disorder (70). When focusing only on patients diagnosed with psychotic depression, it has been found that conversion to bipolar disorder is mainly related to early age at onset (67, 68), functional impairment (67), mixed features (69, 71), and previous hypomanic symptoms (72).

In summary, parental bipolar disorder, especially early-onset (e.g., <21 years old) parental bipolar disorder, is the most important single risk factor for developing bipolar disorder. In addition, if the youth has subsyndromal manic symptoms, which is the most consistent prodromal factor, and ongoing mood lability or irritability, anxiety, and depression, there is increased likelihood that this youth will develop bipolar disorder (Figure 2). However, the onset and severity of these symptoms are heterogeneous.

HELPING PREDICTION OF BIPOLAR DISORDER ONSET THROUGH SCREENING TOOLS

The above predictors are based on studies that focus on groups as a whole, but they do not inform about the individual risk of developing bipolar disorder. Moreover, the prodromal symptoms are heterogeneous, requiring the assessment of each individual risk (64). Building on accumulated knowledge about early bipolar disorder symptoms, researchers have striven to

TABLE 2. Main Findings of Longitudinal Studies Assessing Prodromal Symptoms in Offspring of Patients With Bipolar Disorder[a]

Authors	Mean Follow-Up	N at Baseline (M/F)	Mean Age at Baseline (years)	Offspring Sample Description	Main Objectives
Pittsburgh Bipolar Offspring Study					
Axelson et al., 2015 (49)	6, 8 years	BO: 391 (200/191), CO: 248 (114/134)	BO: 11.9 (SD 3.7), CO: 11.8 (SD 3.6)	Offspring of patients with BD I or II	To study diagnostic differences between BO and CO; to describe the developmental trajectory of mood episodes and identify diagnostic precursors of full-threshold BD in BO
Levenson et al., 2015 (56)	Not stated	BO: 386 (190/196), CO: 301 (144/157)	BO: 11.4 (SD 3.6), CO: 11.0 (SD 3.5)	Offspring of patients with BD I or II	To evaluate baseline sleep and circadian phenotypes in BO and CO; to evaluate whether baseline sleep and circadian phenotypes in the BO are associated with future conversion to BD
Hafeman et al., 2016 (45)	Not stated	BO: 359 (176/183), CO: 220 (99/121)	BO: 11.6 (SD 3.6), CO: 11.7 (SD 3.4)	Offspring of patients with BD I or II	To assess dimensional symptomatic predictors of new-onset BSD in BO
Dutch Bipolar Offspring Study					
Mesman et al., 2013 (52)	12 years	BO: 108 (58/50)	BO: 16.5 (SD 2.00)	Offspring of parents with BD I or II and age 12 to 21 years	To provide data on the onset and developmental trajectories of mood disorders and other psychopathology in BO
Mesman et al., 2017 (61)	12 years	BO: 107 (57/50)	BO: 16 (range 12–21)	Offspring of parents with BD I or II and age 12 to 21 years	To identify early symptomatic signs of BD in BO with a history of mood disorder (any mood disorder group); to explore the early symptomatic signs of first mood episode development in BO without a history of mood disorder (no mood disorder group)

Assessment Tools	Conversion Rate to BSD	Main Findings	Offspring Exclusion Criteria	Limitations
SCID, K-SADS-PL; subthreshold (hypo)mania was diagnosed using the BDNOS criteria from the COBY study, FH-RDC, the Hollingshead scale (SES)	9.2%	There was a higher prevalence of BSD and MDE in BO as compared with CO. Nearly all non-mood axis I disorders were more prevalent in BO than in CO. Mania/hypomania was almost always preceded by mood and non-mood disorders. Distinct subthreshold episodes of (hypo)mania were the strongest predictor of progression to full threshold mania/hypomania in BO.	Mental retardation	The information collected for the interval between evaluations was retrospective; most offspring were not through the age of risk for onset of BD at their last assessment; low conversion rate; only a small proportion of the biological coparents had direct diagnostic interviews.
SCID, K-SADS-PL; subthreshold (hypo)mania was diagnosed using the BDNOS criteria from the COBY study, PDS, Tanner stages, Hollingshead scale (SES), SSHS	Not stated	Conversion to BSD among BD was significantly predicted by parental and child ratings of child frequent nighttime awakenings, by parental ratings of inadequate sleep, and by child report of time to fall asleep on weekends.	Mental retardation	Use of questionnaire-based proxy measures of sleep and circadian phenotypes; long average time span between baseline SSHS and conversion to BD; low conversion rate; cross-sectional nature of the analyses.
FH-RDC, SCID, K-SADS-PL, CALS, CBCL, CADS, CHI, DBD, MFQ, SCARED, Hollingshead Four-Factor Index (SES); subthreshold (hypo)mania was diagnosed using the BDNOS criteria from the COBY study	14.7%	The most important prospective dimensional predictors of new-onset BSD disorders were anxiety/depressive symptoms (baseline), affective lability (baseline and proximal), and subthreshold manic symptoms (proximal). There was an increased risk of new-onset BSD with earlier parental age at mood disorder onset.	Mental retardation	Follow-up visits every 2 years; low conversion rates; not all offspring were through the age of risk for onset of bipolar illness at their last assessment.
K-SADS-PL, SCID	13% (3% BD I)	72% of BO developed psychopathology. In 88% of offspring with a BSD, the index episode was an MDE. In total, 24% of offspring with a UMD developed a BSD. Mood disorders were often recurrent, with high comorbidity rates, and started before age 25.	Children with a severe physical disease or disability or with an IQ below 70	Small sample size; low generalizability to populations without familial risk; no control group; no data on prepubertal and early adolescent disorders or episodes; not assessing for BDNOS.
K-SADS-PL	2.6% (BD II) in the no mood disorder group, 34% (BD I and II) in the any mood disorder group	Subthreshold manic symptoms were the strongest predictor of BD onset in the any mood disorder BO group. Subthreshold depressive symptomatology was associated with first mood disorder onset.	Children with a severe physical disease or disability or with an IQ below 70	Small sample size; low generalizability to populations without familial risk; only the baseline screen items of the K-SADS-PL were used.

continued

TABLE 2, *continued*

Authors	Mean Follow-Up	N at Baseline (M/F)	Mean Age at Baseline (years)	Offspring Sample Description	Main Objectives
Canadian Bipolar Offspring					
Duffy et al., 2013 (54)	6.23 years	BO: 229 (93/136), CO: 86 (36/50)	BO: 16.35 (SD 5.34), CO: 14.71 (SD 2.26)	Offspring with only one parent with a diagnosis of BD I or II and no other major psychiatric comorbidity	To describe the cumulative incidence of anxiety disorders in BO compared with CO; to identify predictors of anxiety disorders in BO; to determine the association between antecedent anxiety disorders and subsequent mood disorders in BO
Duffy et al., 2014 (38)	6.29 years	BO: 229 (92/137), CO: 86 (36/50)	BO: 16.35 (SD 5.34), CO: 14.71 (SD 2.25)	Offspring with only one parent with a diagnosis of BD I or II and no other major psychiatric comorbidity	To estimate the differential risk of lifetime psychopathology between BO and CO; to compare the clinical course of mood disorders between BO subgroups (defined by the lithium response of the parent)
Other offspring cohorts					
Akiskal et al., 1985 (53)	3 years	BO: 68 (39/29)	Not stated	Individuals with a parent or older sibling with BD I, less than 24 years old at intake, and looking for clinical attention within approximately 1 year of onset of psychopathologic manifestations	To chart the prospective course of early manifestations in the referred juvenile relatives of known bipolar adults
Carlson et al., 1993 (51)	3 years	BO: 125, CO: 108	BO: 7–16 years	Children of parents with BD	To examine the relationship between attention and behavioral disorders in childhood and subsequent BD
Egeland et al., 2012 (50)	16 years	BO: 115, CO: 106	Not stated	BO from the CARE study in preschool or in school (younger than 14 years old)	To identify the pattern and frequency of prodromal symptoms/behaviors associated with onset of BD I during childhood or adolescence

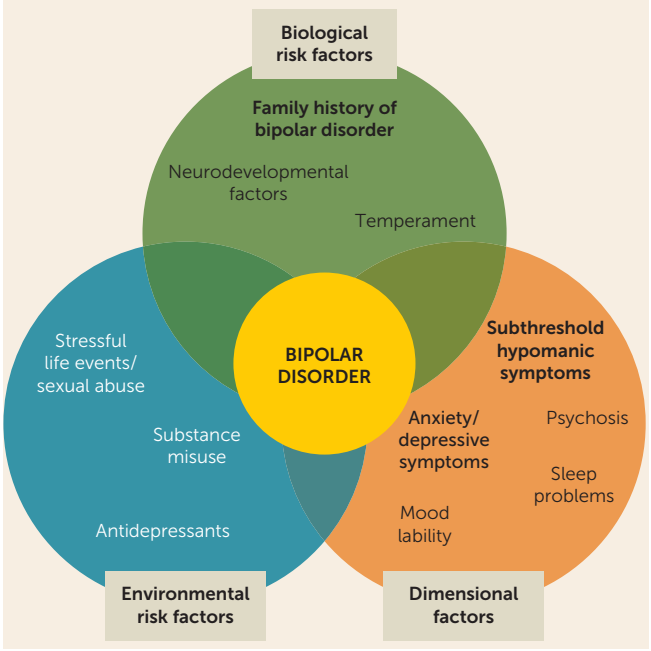
[a] BD=bipolar disorder; BDNOS=bipolar disorder not otherwise specified; BO=bipolar offspring; BSD=bipolar spectrum disorder; CADS=Childhood Affective Dysregulation Scale; CALS=Child Affective Lability Scale; CARE=Children and Adolescent Research Evaluation; CBCL=Child Behavior Checklist; CECA.Q=Childhood Experiences of Care and Abuse Questionnaire; CHI=Children's Hostility Inventory; CO=control offspring; COBY=Course and Outcome of Bipolar Youth; DBD=Disruptive Behavioral Disorders Rating Scale; DBRS=Devereux School Behavior Rating Scales; EAS=Early Adolescent Temperament Scale; FH-RDC=Family History–Research Diagnostic Criteria; GAS=Global Assessment Scale; HARS=Hamilton Anxiety Rating Scale; K-SADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version; MCDQ=Mood Clinic Data Questionnaire; MDD=major depressive disorder; MDE=major depressive episode; MFQ=Mood and Feelings Questionnaire; PDS=Petersen Pubertal Developmental Scale; SADS-L=Schedule for Affective Disorders–Present and Lifetime; SCARED=Screen for Child Anxiety Related Disorders; SCAS=Spence Children's Anxiety Rating Scale; SCID=Structured Clinical Interview for DSM-IV Axis I Disorders; SES=socioeconomic status; SSHS=School Sleep Habits Survey; SUD=substance use disorder; UMD=unipolar mood disorder.

Assessment Tools	Conversion Rate to BSD	Main Findings	Offspring Exclusion Criteria	Limitations
K-SADS-PL, HARS, SCAS, Hollingshead SES scale, EAS, CECA.Q	14%	The cumulative incidence of anxiety disorders was higher and occurred earlier in BO compared with CO. High emotionality and shyness increased the risk of anxiety disorders. Anxiety disorders increased the adjusted risk of mood disorders.	Not stated	Low conversion rate; anxiety disorders preceded mainly MDD; some BO were affected with a mood diagnosis before completing the temperament measure; some offspring were not through the age of risk for onset of bipolar illness at their last assessment.
K-SADS-PL, HARS, SCAS, Hollingshead SES scale, EAS, CECA.Q	13.54%	The adjusted cumulative incidence of BD was higher in BO than CO. There were no differences in lifetime risk of mood disorders between BO subgroups, except for schizoaffective disorder (all cases occurred in BO of lithium nonresponder parents).	Not stated	Retrospective data collection in some offspring; difficult to mask to family affiliation.
MCDQ, the Washington University schema	57%	Acute depressive episodes and dysthymic–cyclothymic disorders are the most common psychopathologic features in the BO. Manic onset occurred after age 13.	Any first-degree relative with schizophrenia	No control group; influence of age at onset of parental illness and type of parental illness not assessed.
Pupil Evaluation Inventory–Peers, ASSESS-Peers, DBRS- Teachers, DBRS- Mother and Father, the distractibility index of the digit span task, SADS-L, SCID (DSM-III), Social and Occupational Competence, GAS, bipolarity rating, SUD rating	4.8%	In childhood, mild to moderate attention and behavior problems were significantly more frequent in BO than in CO. In young adulthood, fewer than half of the BO were free of significant psychopathology.	Not stated	Not stated
CARE Interview instrument	7.8% (BD I)	Higher conversion rates among BO. BO who converted to BD I showed a higher frequency of sensitivity, crying, hyperalertness, anxiety/ worry, and somatic complaints during preschool years and of mood and energy changes, decreased sleep, and fearfulness during school years.		Small sample size; nonstandard interview instrument

FIGURE 1. Main Risk Factors of Conversion From Major Depressive Disorder to Bipolar Disorder

Risk Factors for Conversion
Family History of Bipolar Disorder
Early Onset
Atypical Features
Psychomotor Retardation
Psychotic Symptoms
Functional Impairment
Mixed Features
Previous Hypomanic Symptoms

FIGURE 2. Putative Risk Factors and Prodromal Symptoms of Bipolar Disorder[a]



[a] Several environmental risk factors for bipolar disorder have been proposed, such as stressful life events including sexual abuse, antidepressant use, or substance misuse like cocaine or alcohol misuse. Biological risk factors include family history of bipolar disorder or neurodevelopmental factors such as child developmental delay. Family history of bipolar disorder is one of the strongest risk factors for bipolar disorder, while sexual abuse has been consistently related to a worse illness course. Prodromal symptoms of bipolar disorder can be heterogeneous. Dimensional factors predictive of bipolar disorder include anxiety and depressive symptoms, mood lability, and psychosis or subjective sleep problems, but the most robust predictive factor is the presence of subthreshold (hypo)manic symptoms. Depressive episodes with an early onset and/or psychotic symptoms also seem to predict conversion to bipolar disorder. The interaction between risk factors and prodromal symptoms may lead to bipolar disorder, but the exact mechanisms remain unknown.

design reliable screening tests and screening criteria that could help to predict conversion to bipolar disorder. However, reliable clinical scales to assess prodromal symptoms are still lacking. To date, the predictive value of four clinical scales has been tested in longitudinal studies: the General Behavior Inventory, a self-report measure useful to discriminate between mood and behavioral disorders; the Child Behavior Checklist–Pediatric Bipolar Disorder, a profile consisting of severe aggression, inattention, and mood instability; the Hypomanic Personality Scale; and the Hypomania Checklist–32 Revised scale (73–78). Higher scores on the depression scale of the General Behavior Inventory (74), higher scores on the Hypomanic Personality Scale (75, 76), and positive subthreshold hypomanic symptoms identified by the Hypomania Checklist–32 (77) were related to an increased risk of future mood disorder among bipolar offspring. In turn, the Child Behavior Checklist–Bipolar seems useful for predicting comorbid and impairing psychopathology rather than any one specific DSM-IV diagnosis (73, 78). It is worth mentioning that most participants without the Child Behavior Checklist–Bipolar phenotype did not manifest bipolar disorder, attention deficit hyperactivity disorder (ADHD), cluster B personality disorder, or multiple psychiatric comorbid conditions at young-adult follow-up assessment (negative predictive values of 86% to 95%) (78). An abbreviated version of the General Behavior Inventory, the Seven Up Seven Down, has also been proposed, but it failed to predict new onset of bipolar disorder (79).

Nevertheless, the combination of self-reports and clinical semistructured interviews might be a more accurate approach for clinical decision making than the use of a single scale. Moreover, the assessment of subsyndromal manic symptoms requires trained professionals, as subsyndromal symptoms are difficult to ascertain when assessing children or if comorbid disorders are present. When considering self-report measures, much discussion of the ideal informant has taken place (i.e., parents, offspring, or both), but findings consistently show the greatest validity for parent report, regardless of whether the parent has a diagnosis of mood disorder—one reason being that the degree of awareness of one's own symptoms can influence youth self-report (80).

Besides these proposed screening tests, a set of ultra-high-risk criteria for bipolar disorder exists: the bipolar at-risk criteria developed by Bechdolf et al. (81). They comprise general criteria, such as being in the peak age range for the onset of the disorder, as well as subthreshold clinical and behavioral data and genetic risk. In a sample of help-seeking youths, individuals meeting the bipolar at-risk criteria transitioned significantly more to first-episode (hypo)mania than the group screening negative for the criteria (81). However, important potentially differentiating features such as Mitchell's bipolar signature, including features such as psychomotor-retarded melancholia and atypical depression, are not explored in many risk indices (82). The Early Phase Inventory for Bipolar Disorders criteria (83) and the Bipolar Prodrome Symptom Scale, based on the At Risk for Mania Syndrome criteria (84), are promising screening tools, but they still need to be prospectively tested.

Similar to the existing risk calculators in medicine, the Pittsburgh Bipolar Offspring Study developed a risk calculator to predict the 5-year risk of developing bipolar disorder in offspring of parents with bipolar disorder (85). Including dimensional measures of mania, depression, anxiety, and mood lability; psychosocial functioning; and parental age of mood

disorder, the model predicted onset of bipolar disorder with an area under the curve of 0.76. If replicated, in the future the risk calculator will be instrumental in the development of preventive treatments as well as for biological studies.

HELPING PREDICTION OF BIPOLAR DISORDER ONSET THROUGH BIOMARKERS

Biological and behavioral biomarkers hold promise as objective and useful tools for identifying patients at higher risk of developing bipolar disorder (86). Although biomarkers and staging have not yet had an impact on the official classificatory systems for mental disorders, this is a stated goal of the DSM series (87).

Neuroimaging Biomarkers

In a sample of 98 young unaffected individuals at high familial risk of bipolar disorder and 58 healthy control subjects, the presence of maintained increased insula activation during a task involving executive and language processing could differentiate individuals at high risk of bipolar disorder who later develop depression from healthy control subjects and from those at high familial risk who did not develop a psychiatric disorder (88). Mourão-Miranda et al. (89) showed that the combination of machine learning techniques and functional MRI data collected during an emotional face gender-labeling task could not only discriminate control adolescents from bipolar offspring but also could be helpful in predicting which at-risk adolescents would eventually develop psychiatric disorders. Regarding differences between offspring of parents with schizophrenia and offspring of parents with bipolar disorder, Sugranyes et al. (90) found through repeated neuroimaging measures that schizophrenia offspring displayed cross-sectional reductions in surface area on the occipital lobe compared with bipolar offspring and community control subjects.

Peripheral Biomarkers

Antithyroid peroxidase antibody positivity (91), salivary cortisol levels (92), and cerebral metabolite concentrations measured by proton magnetic resonance spectroscopy (93) could not differentiate high-risk offspring from control offspring or predict conversion to bipolar disorder. However, preliminary findings from the Dutch Bipolar Offspring Study indicate that the monocytes of a large proportion of bipolar patients and their offspring, particularly those who later develop a mood disorder, aberrantly express messenger RNAs of inflammatory, trafficking, survival, and mitogen-activated protein kinase pathway genes compared with healthy control subjects (94). This aberrant neuroimmune state in bipolar offspring was found to be independent of lifetime or future mood disorders; hence, it might reveal a vulnerability for mood disorders rather than being a direct predictor (95, 96). In a prospective general-population U.K. birth cohort childhood study, higher levels of the systemic inflammatory marker IL-6 in childhood were associated with hypomanic symptoms in young adulthood, even after adjusting for sociodemographic variables, past psychological and behavioral problems, body mass index, and maternal postnatal depression (97).

Nevertheless, most of the identified alterations in peripheral blood in ultra-high-risk populations are shared between different psychiatric disorders, potentially predicting the onset of bipolar disorder, depression, or schizophrenia, but alone they are not able to reliably predict occurrence of bipolar disorder over another disorder. One study proposed a blood-based biomarker panel for diagnosing bipolar disorder, employing several different biomarkers. This panel, consisting mostly of immune-related biomarkers, was able to discriminate between recently diagnosed (less than 30 days) bipolar disorder and both recently diagnosed schizophrenia and healthy control subjects (60). This suggests that a single blood biomarker will likely not be useful for ascertaining diagnosis, but that a composite of several biomarkers, and probably other sources of information, will be required in order to achieve sufficient diagnostic properties for clinical utility.

Behavioral Biomarkers

A newly emerging biomarker in the form of ecological momentary assessment is arising from the ability to track behavioral data through mobile devices (98, 99). Hence, big data, such as geolocation, activity, Internet use, calls, and payments, can be analyzed and provide algorithms that might be used through machine learning techniques (100) as sources for risk surveillance and hence early personalized interventions (101).

EXPLORING EARLY TREATMENT STRATEGIES IN BIPOLAR DISORDER

The underlying tenet of early diagnosis is to implement early treatment in order to prevent or delay progression to more advanced stages of the disease associated with greater disability (102). However, there are critical ethical issues pertaining to preventive interventions in at-risk individuals. Potential benefits need to be balanced against risks of preonset interventions. Key considerations include the individual's knowledge, autonomy, and right to choose, ideally in an environment of stigma-free treatment (103).

Effective psychotherapeutic interventions, usually better received by patients and with a more favorable benefit–risk profile, can be an attractive first step in early intervention, although their effectiveness at these early stages needs to be determined (83). Post hoc analysis of many psychosocial interventions for bipolar disorder suggested greater efficacy if used earlier in the illness course (104). Psychoeducation programs have proven effective in preventing relapse in patients with established bipolar disorder and may be more useful earlier in the disorder (105, 106), but they have not been assessed in at-risk populations or pediatric bipolar disorder. Hence, group psychoeducation may be particularly indicated in patients with an established diagnosis of bipolar disorder but with a limited number of recurrences (107). Family-focused therapy, which combines psychoeducation sessions and training in communication and problem-solving skills, is the only psychological

intervention tested in these populations. Results on this therapy are still controversial, although they suggest that it is related to longer affective stability and milder symptoms during follow-up (108, 109) when assessed in youths at high familial risk for bipolar disorder and diagnosis of bipolar disorder not otherwise specified, major depressive disorder, or cyclothymic disorder, or in adolescents with bipolar I or II disorder. Other interventions, such as multifamily psychoeducational psychotherapy (110) or interpersonal and social rhythm therapy (111), have shown some preliminary but promising results in reducing conversion rates and symptom severity among high-risk adolescents with a positive family history of bipolar disorder. Psychotherapies are not free of side effects (112); at early stages, when the diagnosis is not established, emphasis on diagnoses should be avoided, and it is more useful to target identified symptoms and helpful strategies (113). A number of online psychosocial interventions that are increasingly available have tentative data regarding their effectiveness (114, 115).

Choosing preventive pharmacological treatments in at-risk individuals is particularly complex. In the at-risk stage, we may be treating a population that might not convert to bipolar disorder, and the treatment of prodromal symptoms or comorbid conditions may involve medications with a potential risk of precipitating a manic episode, such as psychostimulants or notably antidepressants. Hence, even though some pharmacological treatments, such as lithium, are known to be more effective when started early in the course of the disease (116), the long- and short-term tolerability of each treatment and its potential to prevent bipolar disorder need to be carefully weighed against the individual risk of developing bipolar disorder. Some pilot studies have assessed the protective properties of valproate sodium and quetiapine against the onset of mania, with mixed results (117–119). Moreover, treatment with mood stabilizers or antipsychotics has known short- and long-term adverse effects (120), so their use as first-line treatment in at-risk youths might not be recommendable (121). For instance, valproate sodium has been associated with reproductive–endocrine abnormalities and should be used with caution in women of childbearing age (122, 123). Another scenario is posed when it comes to youths with bipolar disorder not otherwise specified. These youths have as much psychosocial impairment, as many comorbid disorders, and as much risk for suicide and substance abuse as those with bipolar disorder I, and they are at high risk of converting to bipolar I or II disorder (62, 124). Thus, until further research is available, we recommend treating them with the existing psychological and pharmacological treatments for youths with bipolar disorder, depending on factors such as the impact of the symptoms on the youth's functioning and well-being and the individual risk of converting to bipolar I or II disorder.

Considering the feasibility of using nutritional supplements for primary prevention and the reported link between folate deficiency or omega-3 fatty acids and mood symptoms, these compounds have been proposed as a possible treatment in at-risk samples (121, 125). However, in a double-blind parallel-group placebo-controlled trial, Sharpley et al. (125) did not find any impact of folic acid supplementation on the incidence of mood disorder in a youth sample at increased familial risk of mood disorder. Post hoc analysis, though, suggested that folic acid might help to delay the time to onset of mood disorder (125). A recent study reported that omega-3 fatty acids failed to prevent conversion from at-risk mental state to threshold psychosis (126), yet results are limited by the low conversion rate in the placebo group. Thus, the efficacy of omega-3 fatty acids in high-risk populations needs further investigation (127). Anti-inflammatory strategies such as aspirin have demonstrated potential to reduce risk of depression in epidemiological studies. Aspirin is being explored as a potential preventive strategy for depression in a very large clinical trial of over 19,000 people (128). Hence, examining the potential protective effects of nutritional and tolerable pharmacological supplements remains a promising line of research (121). Potential treatments for cognitive dysfunction (cognitive enhancers) might come up in the near future and pose new ethical questions as to when and in whom to use them (129).

Regarding predictors of treatment response, there are no solid results yet (130, 131), but reported results do suggest a number of regions meriting further investigation, such as the gene coding for a subunit of the ligand-gated ionotropic glutamate receptor, GluR2/GLURB (131). A recent genome-wide study from the International Consortium on Lithium Genetics of 2,563 patients found a single locus of four linked single-nucleotide polymorphisms on chromosome 21 that met genome-wide significance criteria for association with lithium response (132). Furthermore, in an independent prospective study of 73 patients treated with lithium monotherapy for a period of up to 2 years, carrying the response-associated alleles was associated with a significantly lower rate of relapse (132). The pharmacogenetics of pharmacodynamic pathways, such as P450 enzymes and blood-brain barrier polymorphisms, is being explored as a predictor of antidepressant response (133), although not yet for mood stabilizers. However, sensitivity and specificity limitations mean that these genetic findings are not yet robust enough to guide treatment decisions.

SUMMARY AND FUTURE DIRECTIONS

The findings of this review support the notion of a prodromal state and a progressive course in bipolar disorder. This dynamic course fits in the model of clinical staging proposed by several authors (14, 134–137), which assumes that illnesses progress from an at-risk stage to a late and resistant stage.

A positive family history of bipolar disorder, particularly if the parents have early-onset bipolar disorder, is the most significant risk factor for developing a bipolar spectrum disorder. Regarding prodromal symptoms, the most robust result is that subthreshold (hypo)manic symptoms are the strongest predictor of bipolar conversion, both in studies focusing on bipolar offspring and in community youths. Consequently, this translates into a need for screening for attenuated mania-like symptoms when assessing young patients seeking help for mood lability, anxiety, depression, or

behavioral disorders, especially among bipolar offspring (138). Moreover, preliminary findings indicate that bipolar offspring with an aberrant inflammatory state or changes in the volume or activity of the amygdala may be more vulnerable to developing a mood disorder, suggesting a potential role for these alterations as putative biomarkers for disease prediction in individuals at genetic risk (121, 139).

However, even if there is a promising emerging set of putative prodromal symptoms, biomarkers, and environmental risk factors, the possible additive or synergistic associations between all these factors remains a mystery (121). Therefore, more studies are needed to build a clear picture of high-risk bipolar states that can help clinicians differentiate genuinely at-risk individuals from persons with benign and self-limiting states (140, 141). Moreover, since prodromal symptoms are highly heterogeneous and particular to each individual, individualized risk assessment is needed. Novel bioinformatic techniques, such as machine learning approaches, present a valuable ally in the field of early intervention to overcome such limitations (142, 143).

Early intervention is an ideal breeding ground for new randomized clinical trials looking for the most efficacious treatment strategy for early stages. Currently there are no specific treatments for symptomatic youths who do not fulfill diagnostic criteria for bipolar disorder not otherwise specified but are at very high risk of developing bipolar disorder because one or both of the parents are diagnosed with bipolar disorder, particularly early-onset bipolar disorder. Since these children already present psychopathology in the form of symptoms of depression, anxiety, mood lability, or subsyndromal mania, they require existing treatments to target these symptoms—either pharmacotherapy or psychological therapies such as cognitive-behavioral therapies, family-focused therapy, self-help programs, or mental health first aid. What we do not know yet is whether these treatments will also prevent the onset of bipolar disorder. Thus, the need to perform studies to prevent or at least delay the onset of bipolar disorder should be considered a priority in psychiatry, especially in countries with a higher prevalence of pediatric bipolar disorder (144). Furthermore, as pointed out by Lambert et al. (145), once the most efficacious therapy is identified, further efforts should be made to ensure that at-risk populations have access to these interventions. Providing specialty care in youth mental health clinical services may be preferable to standard outpatient care, as evidence suggests that specialized treatment is more clinically effective and cost-effective (146, 147). Very gradual dosage escalation and cautious use of pharmacotherapy, potentially augmented by pharmacogenetics if positive data emerge, may help treatment choice when pharmacological treatment becomes necessary. In the early stages, prevention of potential side effects is paramount, since an initial adverse experience primes beliefs about medication and powerfully influences future adherence and engagement (148). In the case of bipolar disorder, there is some indication that critical factors for illness outcome, such as cognitive impairment, are heavily influenced by illness course and morbidity (149, 150). Hence, the early implementation of prevention strategies as appropriate according to illness stage and clinical phenotype may already help in preventing functional impairment. For very early stages, promoting and enhancing cognitive reserve may be one way to go (151–154).

Early intervention strategies in bipolar disorder face the lack of specificity of prodromal symptoms, as evidence emerging from studies performed in populations at ultra-high risk for psychosis indicate that there might be a common risk syndrome for diverse major psychiatric illnesses prior to the development of full symptoms more characteristic of any particular disease (141). Fernandes and Berk (142) hypothesized that this might also be true for biomarkers, with biomarkers useful for staging being common across different psychiatric disorders. Indeed, many of the biomarkers found in populations at risk for bipolar disorder are predictive for major psychiatric disorders in general and are common across commonly comorbid noncommunicable medical disorders, such as diabetes and cardiovascular disorders. This raises the question of whether more general interventions oriented toward enhancing stress-management strategies or reducing the proinflammatory state identified in at-risk individuals should be preferable. Findings concerning neurodevelopment, though, indicate that there may already be subtle potential differences between some psychiatric diseases at the earliest stages (155). In any case, this highlights the urgency of performing studies to test whether any given early intervention would help reduce vulnerability to psychiatric illnesses in general and not only to bipolar disorder, as bipolar offspring are at high risk of developing a wide range of psychiatric illnesses. As mentioned before, testing the protective potential of a variety of psychological interventions such as cognitive-behavioral therapies, family-focused therapy, self-help programs, or mental health first aid, or compounds such as omega-3 fatty acids, *N*-acetylcysteine, or minocycline, might be a feasible line of research. Lifestyle modifications such as smoking cessation, encouragement of physical activity, and healthy diet are indicated across the psychiatric spectrum and commonly comorbid medical disorders as well (156).

Overall, this review supports the idea of the existence of an at-risk state in bipolar disorder, thereby laying the foundations for bringing early intervention to life. However, we cannot deny that further efforts are required to advance on the difficult road of primary prevention. Given that psychiatric and commonly comorbid medical disorders share common risk determinants and operative biological pathways, a shared framework for disease prevention and control is warranted. A cross-disciplinary, multitarget approach is essential for wide-scale implementation in real-world settings (156). The need for new prospective studies with a larger sample size and standardized recruitment criteria and assessment tools is unquestionable. These studies should assess the validity of the proposed predictive factors to better determine which individuals are at highest risk for conversion and therefore more likely to benefit from early interventions. Further studies

on early psychological and pharmacological interventions, either alone or in combination, are equally warranted.

In conclusion, considering that the onset of bipolar disorder usually occurs during adolescence—a period of personal, social, and professional development that is often truncated by the illness—introducing early interventions in psychiatry is imperative. By the time *The American Journal of Psychiatry* commemorates its 200th year of publication, we look forward to seeing that early intervention in psychiatry has been integrated in common clinical practice.

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