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Early interventions for youths at high risk for bipolar disorder: A developmental approach

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Abstract

In recent decades, ongoing research programs on primary prevention and early identification of bipolar disorder (BD) have been developed. The aim of this article is to review the principal forms of evidence that support preventive interventions for BD in children and adolescents and the main challenges associated with these programs. We performed a literature review of the main computerised databases (MEDLINE, PUBMED) and a manual search of the literature relevant to prospective and retrospective studies of prodromal symptoms, premorbid stages, risk factors, and early intervention programs for BD. Genetic and environmental risk factors of BD were identified. Most of the algorithms used to measure the risk of developing BD and the early interventions programs focused on the familial risk. The prodromal signs varied greatly and were age-dependent. During adolescence, depressive episodes associated with genetic or environmental risk factors predicted the onset of hypomanic/manic episodes over subsequent years. In prepubertal children, the lack of specificity of clinical markers and difficulties in mood assessment were seen as impeding preventive interventions at these ages. Despite encouraging results, biomarkers have not thus far been sufficiently validated in youth samples to serve as screening tools for prevention. Additional longitudinal studies in youths at high risk of developing BD should include repeated measures of putative biomarkers. Staging models have been developed as an integrative approach to specify the individual level of risk based on clinical (e.g., prodromal symptoms and familial history of BD) and non-clinical (e.g., biomarkers and neuroimaging) data. However, there is still a lack of empirically validated studies that measure the benefits of using these models to design preventive intervention programs.

Keywords: Early onset bipolar disorder; high-risk study; prevention; early intervention; children; staging models

Introduction

Over the past few decades, preventive interventions have been proposed to prevent or limit the consequences of bipolar disorder (BD) in adults. Because more than half of adult patients with BD present their first episode before the age of 18 [1,2], these programs would mainly concern children and adolescents. This concern is of particular importance with regard to the high level of functional impairment in affected children and adolescents. BD is the fourth leading cause of disability among youths aged 10-24 worldwide and is associated with an increased risk of suicide [3,4]. In this paper, the evidence that supports the development of such interventions at these ages is discussed. First, to understand the growing interest in the development of a preventive approach, the natural course of BD is discussed. Second, we examine whether the following criteria for the development of an effective prevention of BD in paediatric samples have been met: (i) genetic and environmental risk factors for BD must be identified in view of defining a target population; (ii) clinical markers that predict the onset and/or the course of the disease must be determined; (iii) endophenotypes or biomarkers that reflect an early pathological process could help to identify individuals who require special attention, and (iv) the effectiveness of preventive interventions must be evaluated. Finally, the use of staging models that were previously developed for psychosis, has been proposed for BD. These models were conceived as tools based on clinical (e.g., symptoms and family history of BD) and non-clinical (e.g., neuroimaging and biological markers) parameters for measuring the risk of progression over the course of the disease. It is

seen as a rational approach to adapting treatments with potential side-effects to a specific situation according to the individual level of risk. However, despite a theoretical framework that supports the use of staging models in BD, few studies have examined the empirical evidence. This review will examine the internal and external validity of models that focus on the transition from a non-symptomatic at-risk status to the first manic episode.

1. The life-time course of bipolar disorder

Although BD has traditionally been described as a cyclical disorder with euthymic periods, in recent decades, the clinical importance of inter-episode symptoms has been highlighted. It has been noted that symptom-free periods are actually rare in bipolar patients, who continue to report subsyndromal affective symptoms between episodes [5]. An aggravation of the disease with more severe symptoms and shorter periods between relapse is observed throughout the course of BD in a sizeable proportion of patients [6-9]. The concepts of *kindling* and *neuro sensitisation* were coined to describe the phenomenon of a progressive increase in episode frequencies as the mood episodes repeated [8,9]. Although this concept have largely been cited in support of the promotion of early interventions in BD, this assumption has been contradicted by empirical evidences [10,11]. In a 30 year follow-up study among outpatients with BD (N=220), Angst and Sellero found that a shortening of cycle length only occurred in the first few, but not in later episodes [10]. In addition to subthreshold symptoms, some degree of cognitive impairment also persists during euthymic periods in patients with BD [12-14]. Increasing cognitive difficulties have been reported over the course of the disorder and are correlated with the number of manic episodes [15]. Longitudinal studies in adults have supported the assumption that inter-episode functioning

decreases as the disease progresses in most individuals with BD [16,17,6]. This progressive course is seen as a key factor in explaining the poorer functional outcomes in BD patients with delayed treatment compared with others [1,2,18]. Indeed, patients with a prolonged phase of untreated illness report on average a lower rate of employment [19], a higher number of hospitalisations [20], more forensic complications, and a higher level of functional impairment [3,21]. The view of BD as both a progressive and cyclical disease is also supported by different responses to treatment observed according to the stages of the illness [6,9,18]. The number of manic episodes that a patient experiences has been associated with greater resistance to pharmacological treatment [8,9,22]. However, these findings were not replicated when the response to lithium was examined in a large 20-year follow-up study among adults with BD [23]. Concerning psychological interventions, cognitive behavioural therapy (CBT) and psychoeducational therapy have shown more effectiveness in the early stages of the disease compared with the later stages [24-26]. However, a meta-analysis found that the number of previous thymic episodes had no impact on psychotherapeutic effectiveness [27]. These conflicting results could stem from the heterogeneity of BD in terms of the illness course and treatment response [28,29]. Preventive interventions would aim to reverse or slow the life-time course of BD, in particular in those who present severe disease progression. In the next section, the criteria that are required for the development of such programs for BD in children and adolescents will be examined.

2. Criteria for the development of effective preventive interventions in the paediatric population

(i) Genetic and environmental risk factors

If a preventive strategy is to be developed, genetic and non-genetic risk factors must be determined to identify sub-groups that are at high risk of BD transition. Table 1 presents the main risk factors that have been identified for the onset and progression of BD.

Genetic factors

A positive family history of BD is the strongest independent risk factor for the development of related mood disorders [30,31]. Twin and family studies have reported a 59-87% heritability of BD, and the concordance rates between identical twins range from 40 to 97% [32]. Based on the DSM-IV criteria for BD-I and BD-II, first-degree relatives have a 23% chance of developing a mood disorder; within this 23%, the chance of developing a form of BD is approximately 9% [30]. Considering the high heritability rate, the offspring of BD parents appear to be good candidates for determining the efficacy of early intervention strategies. However, it should be mentioned that such an approach would omit subjects who do not have first-degree relatives with BD.

Environmental factors

In addition to genetic predisposition, some environmental risk factors could impact the life-time course of BD. Approximately 50% of BD patients have histories of severe trauma or abuse during childhood [33]. In retrospective studies and prospective outpatient studies, early sexual abuse has been associated with an earlier age of BD onset, a greater frequency of comorbidities, increased symptom severity and suicidal ideation, an increased number of mood episodes, and greater treatment resistance [33-35]. For example, Geller et al. found that

low ratings of maternal warmth and greater parent-child conflict are associated with earlier recurrences over four years among childhood and preadolescent bipolar patients [33]. The poorer course of bipolar youths who were exposed to childhood abuse/neglect has also been supported by epidemiological studies. Data from the National Comorbidity Survey Replication indicated that a history of maltreatment predicted earlier onset and longer episode duration of BP [34]. The dose-effect relationship observed between childhood maltreatment and the severity of BD suggests that adverse life events have an effect across the different stages of the disease [35]. It has been suggested that early adversity mediates the relationship between genetic vulnerability and an early onset of the illness, which in turn predicts a less favourable prognosis [33]. Two general comments are worth mentioning with regard to these findings. On one hand, the association between abuse/neglect and the onset of BD was not investigated in the prospective high-risk studies conducted in the offspring of parents with BD. Thus, regarding maltreatment as a strong prognosis factor does not imply that it should be considered as an independent risk factor for the onset of BD. Moreover the fact that high conversion rates to BD were observed in pediatric sample associated with a low prevalence of abuse and neglect indicates that stressful life events are neither necessary nor sufficient to develop BD [35,36]. The association between BD and maltreatment found in cross-sectional studies of the offspring of parents with BD could partly reflect general difficulties in the parenting practices of adults with BD [36]. On the other hand, it is important to determine whether the results found in outpatient studies were an artefact of the inclusion of youths with dysregulated mood who were misdiagnosed as having BD (such as youths with Disruptive Mood Dysregulation Disorder).

Substance use also impacts the course of BD. Approximately, 60% of individuals with BD will develop substance abuse or dependence [37]. Conversely, substance abuse was reported

to be a risk factor for developing BD in retrospective studies and in prospective studies among the offspring of parents with BD [38,39].

Long-term treatment with antidepressant medications precipitates or exacerbates manic symptoms and reduces the age of onset of mania [40]. A potential risk for episodes of mania induced by stimulant medications was supported by preliminary evidence; but not confirmed by more recent prospective studies [41,42].

[Insert Table 1 about here]

Limitations and further research

Beyond the recognition of environmental and genetic risk factors for BD in children and adolescents, there is still much to be done to understand the interactions between these factors. Some of the identified factors could be inter-correlated (e.g., substance abuse and maltreatment), some factors could be necessary for the development of others, and some factors could simply co-occur. A better understanding of the common pathophysiological pathways that mediate the effect of different risk factors could help to develop effective interventions. For example, Meyer et al. found that the effect of maternal negativity on the early onset of BD among the offspring of mothers with BD was mainly mediated by difficulties in executive cognitive abilities [43]. Finally, the moderating effects of protective factors, such as temperament and social and familial environment, should be better understood.

(ii) Specific clinical symptoms during the prodromal stages

Before detailing prodromal symptoms, several points about methodologic issues are worth noting. Different types of studies have been conducted to determine which symptoms precede the onset of BD. Retrospective studies are surveys in which adult participants describe the symptoms that precede the onset of BD [1,44-46,2]. These retrospective studies have supported the view that a prodromal phase exists in BD during childhood [1,2]. However, methodological biases (such as a recall bias or a lack of precision in estimating the age of onset) make modelling the course of the prodromal symptoms difficult. In contrast, prospective studies provide reliable and detailed data on the course of bipolar prodromal symptoms because clinical symptoms are estimated through repeated assessments of youths prior to the onset of BD. Recent reviews have detailed the prodromal symptoms of BD [47,18]. In this article, we present only the main results from those prospective studies.

Studies of child and adolescent outpatients

Follow-up studies that monitored the rates of diagnostic conversion to BD among outpatient youths with behavioural/emotional problems have been conducted. Typically, subjects are included when their symptoms are severe enough for them or their families to seek admission for assessment and treatment. Consequently, these studies are prone to Berkson bias and a high comorbidity rate is usually reported. The Course and Outcome of Bipolar Youth (COBY) study is a large US prospective outpatient study that included youths with manic symptoms who did not meet the criteria for a diagnosis of maniac/mixed episode (i.e., bipolar disorder not otherwise specified, BD-NOS). The COBY team found that 25% of 92 children

and adolescents with BD-NOS had converted to BD-I or BD-II at a 2-year follow-up [48]. At a 4-year follow-up, 38% of 141 BD-NOS subjects had converted to BD-I or BD-II.

Geller et al. examined the transition to BD among young adults who had participated in a study of pharmacological treatment for childhood depression. At a 10-year follow-up, 49% of 72 subjects with prepubertal major depression had converted to some form of BD [49].

Kochman et al. conducted a 2-year follow-up study in children and adolescents with a major depressive disorder and probands with bipolar disorder. They found that those who presented a combination of elevated mood with irritability and rapid mood fluctuations (labelled *cyclotaxia*) were more likely to develop a manic episode [50].

Akiskal et al. found that “mood lability”, “energy–activity” and “daydreaming” trait factors strongly predicted conversion to BD-II in youths with unipolar depression [51].

Studies in a community-based sample

Longitudinal studies conducted in an unselected community-based sample can facilitate the generalisation of findings. In the Dunedin (New-Zealand) birth cohort (N=922 children), Kim-Cohen et al. found that 74% of the adults with BD presented early signs before 18 and 50% before 15 years. All of the adults who developed BD had already presented a paediatric psychiatric disorder: anxiety disorder, and/or depressive disorder, and/or disruptive disorder [52]. In The Great Smoky Mountains Study (N=717 children), youths who developed BD were more likely to present a psychiatric disorder in adolescence, such as anxiety (OR=20), depressive disorder (OR=5.4), disruptive disorder (OR=6.3) and personality disorder (OR=6.8) [53,54]. In a 15-year follow-up Swedish community-based study (N=2,300), Paaren et al. reported that among adolescents with a major depressive disorder, those with early disruptive disorders or multiple somatic symptoms in childhood were more likely to

develop BD in adulthood (respectively, OR=3.6 and OR=6.6) [55]. In this study, of the 64 adolescents with hypomania spectrum episodes during childhood, only 6 developed a hypomanic/manic episode as adults. Anxiety disorders (panic attack and general anxiety disorder) substantially increase this risk (OR=12.0) [55].

Studies of offspring of parents with BD

As developed earlier, heritability is the most robust risk factor for BD. Therefore, providing data about bipolar prodrome by studying the offspring of probands with BD is a major strategy. In addition to the cost of these studies, the main limitation concerns the generalisation of the findings to youths who do not have a family history of BD.

Akiskal et al. conducted a 3-year follow-up study on youths who were admitted for services and whose parents presented BD. Those who developed BD were more likely to present anxiety, minor mood symptoms and adjustment disorders before the onset of BD [56]. The first mood disturbances were depressive in polarity and occurred before adolescence, whereas mixed and psychotic episodes occurred after puberty.

Hillegers et al. studied the risk of developing BD in a sample of 129 high-risk Dutch adolescents [35]. After 5 years of follow-up, 12 out of the 13 adolescents who developed BD had first presented a depressive episode at adolescence. On average, a hypomanic episode appears 4.9 years after the first depressive episode.

Shaw et al. compared 110 at-risk children who had a BD-I parent to children who had healthy parents in the Amish population. They found a higher frequency of broad spectrum episodic symptoms in offspring of bipolar parents: anxiety, inattention at school, easily excited behaviour, hyper alertness, mood lability, and somatic complaints [57]. A further 5-year follow-up led to determining five additional symptoms in adolescents: variations in sleep and

energy, problems with thinking/concentration, excessive talking, and loud talking [58].

Egeland et al. suggested that the prodromal symptoms of BD would encompass episodic signs before 6 years old (such as crying, anxiety, over sensitivity, somatic complaints) and more adult-like symptoms from 7 to 12 (such as anxiety and variation in sleep and energy, emotional lability, shyness, functional impairment) [58].

Duffy et al. assessed the diagnostic status and conversions to BD after a 4-year follow-up of 127 high-risk offspring [36]. The lifetime prevalence of BD increased from 6% to 20% compared to the offspring from control families. Of 40 offspring with sleep and/or anxiety disorders, 12 developed BD, and 12 developed depressive disorders. The index mood episode in those who developed BD was almost always depression. A history of anxiety was found to increase the risk for the development of any mood disorder from 40% to 85%, approximately 8 years after the beginning of the anxiety symptoms [40]. Similarly, sleep disturbances that preceded BD occurred several years before the onset of the first mood episode. The same team hypothesised that a majority of offspring of bipolar adults who went on to develop BD observed a typical chronological sequence of prodromal symptoms. Among the 207 offspring, approximately 71% of the children who developed BD followed this sequence: non-mood symptoms (i.e., sleep disturbances and anxiety disorder) first appear in the prepubertal child; then, non-specific minor mood symptoms emerge around puberty; the onset of recurrent major depressive episodes occurs later in mid-adolescence; and finally, the first hypomanic/manic episode occurs years later [39].

Axelson et al. examined the risk of developing BD in 391 high-risk offspring aged 6-18 years. After a 6.8-year follow-up, subthreshold manic or hypomanic episodes (OR=2.3), major depressive episodes (OR=2.0), and disruptive behaviour disorders (OR=2.1) were associated with a higher risk of developing BD [59].

Limitations and further research

Based on previous findings, a model has been proposed (Figure 1) to illustrate the course of prodromal symptoms over time in children and adolescents before the onset of BD in young adults. This model highlights the increasing specificity of the prodromal symptoms observed over time and their different predictive values, depending on the stage of development. Two different periods should be distinguished. In prepubertal at-risk children, non-mood (e.g., anxiety) and minor mood (e.g., sleep disturbance) symptoms were associated with a higher transition to BD. Identifying the possible candidates for bipolar preventive intervention based on these symptoms raised two difficulties. First, on a practical level, concerns have been raised regarding the difficulties of distinguishing minor mood symptoms from mood variations within the normal range in the youngest children [60,61]. Second, it is still unclear to what extent these symptoms predict BD, or any other psychiatric disorder (e.g., unipolar depression or psychosis). As suggested by Kim-Cohen et al., bipolar prodromal symptoms are difficult to distinguish from symptoms that precede unipolar depression or psychosis [52]. In addition, the inclusion of paediatric subthreshold manic-like symptoms into the adult bipolar spectrum raised a great deal of controversy [60]. With respect to this issue, the substantial amount of literature that was devoted to the so-called paediatric presentation of BD clarified some issues. Evidence supports that episodic and persistent mood symptoms should be distinguished because only the former predicts BD [62-64]. For example, Stringaris et al. noted that among 84 youths with non-episodic irritability, only one developed hypomanic/manic or mixed episodes over a 2-year follow-up [62]. Similarly, a large amount of longitudinal data supports that persistent and chronic mood symptoms predict unipolar depression and anxiety, but not BD, in adults. Such distinctions have been endorsed by the

recent inclusion of Disruptive Mood Dysregulation in the chapter of depressive disorders in the DSM-5 classificatory systems.

In adolescents, high-risk studies showed that in most cases, affective disturbances begin during adolescence and are depressive in polarity [36,35,57]. Few manic or mixed episodes were reported before puberty, while more than 90% of BD patients presented depressive symptoms in mid-adolescence [65,35]. Certain characteristics of the depressive episode were associated with an increased risk of developing BD: an acute onset [66], a weight gain, somatic preoccupations, a diminished concentration, a predominantly irritable mood [67], psychotic features, severe psychomotor retardation (e.g., Cotard syndrome) [68], and medication-induced hypomanic symptoms [69].

[Insert Figure I about here]

Research on at-risk children for BD highlight two fundamental principles of developmental psychopathology: equifinality and multifinality. Equifinality means that multiple developmental pathways can converge on the same clinical outcome [70]. A large amount of evidence in adults supports that different subtypes of BD with distinct risk factors and clinical courses exist. Such heterogeneity could represent additional difficulty in determining a unique pattern of bipolar prodromal symptoms for all presentations [29,28]. The notion of multifinality reflects the variety of trajectories that could arise from one specific constellation of prodromal symptoms. On the one hand, the lack of specificity of prodromal bipolar symptoms makes the identification of a clear at-risk group based on clinical approach difficult, especially because subthreshold manic and depressive symptoms are much more common in the general population than those for psychosis. On the other hand, a large

overlap between prodromal symptoms for psychosis and for BD have been observed [71]. At this time, preventive programs should focus on the identification of depressive episodes in youths who present with genetic and/or environmental risk factors. Such programs must be considered as a secondary prevention because these symptoms reflect the initial thymic episode as illustrated in Figure I.

(iii) Endophenotypes and biomarkers

Considering the limited specificity of symptoms that are described during the prodromal stages, non-clinical indicators could prove to be valuable in distinguishing youths who are at high risk of developing BD from others. An endophenotype is a heritable biological trait that serves as a marker of risk for a later disorder [72]. Endophenotypes could help to identify individuals who are likely to manifest prodromal states of BD. Biomarkers have been proposed to reflect dysfunctional neurobiological mechanisms that facilitate the onset and progression of BD [73]. Moreover, the identification of such markers could help to define possible targets for preventive approaches.

Temperamental traits

Studies have examined whether specific temperamental traits can confer additional risk of developing BD in vulnerable individuals [74,75,50,76-78]. Most of these studies have compared temperamental features between offsprings of unaffected parents, offspring of bipolar parents with and without psychopathology [75,74,77]. For example, emotionality (defined as an easy tendency to cry and react intensively when upset) was positively

associated with the risk of having a mood disorder in a cohort of offsprings of parents with BD [75]. Doucette et al. [78] examining temperament profiles among offspring of a parent with BD (N=221) found that those who exhibited a high level of emotionality were more likely to develop a mood disorder (OR=1.24) compared to offspring from families with unaffected parent.

A cyclothymic temperament (i.e., with highly mood-lability and emotionally overactive) was found to be a predictor of switching to BD in a population of children and adolescents with major depressive disorder (N=80) in a 2-year follow-up study [50]. Evans et al. [76] confirmed that cyclothymic temperamental traits are present at a higher rate within BD adults than in unaffected relatives of patients with BD, and then in controls.

As noted by Duffy et al. [75], further longitudinal studies of temperament features that predispose to BD could help to a better understanding of the interplay between genetic factors, psychopathology and undesirable life events in youth who later develop BD. Further studies are also needed to determine how these temperament traits cosegregate with BD within families and if it is specific to BD [74].

Endocrine and inflammatory markers

Preliminary studies in this field have explored the role of cortisol and the increased activity in the hypothalamic-pituitary-adrenal (HPA) axis in mood disorders [79]. Subtle abnormalities in the HPA system were found to predict the development of affective disorder. For example, high-risk offspring of parents with BD tend to exhibit higher levels of cortisol during the afternoon compared to low-risk offspring [79]. However, further studies are needed to understand whether cortisol can be considered a marker of vulnerability to BD, an

etiopathological factor, or the biological response to chronic stress in youths who present non-specific emotional/behavioural symptoms. A major focus was placed on markers of neuroinflammation, neurotrophic factors and oxidative stress, considering their putative roles in the pathophysiology of BD [6,73,80,14,81,82]. An increase in the level of peripheral pro-inflammatory markers (such as TNF- α and interleukine-6) and a decrease in the level of circulating brain-derived neurotrophic factor (BDNF) were reported initially during thymic episodes and then during euthymic periods [83-85]. Despite the keen interest in the development of inflammatory markers for BD, caution is required because the main assumptions were extrapolated from studies that were conducted in adults with existing BD. For example, none of the studies of biomarkers in BD that were reviewed in a recent meta-analysis included subjects who were below the age of 18 years [73]. Only two studies have been conducted with paediatric samples. Padmos et al. found that monocyte activation of inflammatory genes predicted the development of mood disorders in adolescent bipolar offspring (n=54) [86]. Mesman et al. conducted a prospective study to examine the evolution of inflammatory biomarkers in 140 children of parents with BD. They found an increased expression of genes that are involved in the inflammatory process during adolescence (e.g., cytokines pentraxin 3), and a decrease in the expression of BDNF [87].

Neurocognitive impairment

When it exists, the neurocognitive impairment that is found in BD usually appears at a late stage of the disease. For example, unlike psychosis disorders, such deficits were not systematically reported after the first acute episode [88]. However, minor deficits in executive function, verbal memory, and attention have been described in unaffected children who are at risk of developing the disease [88-91,43]. Deficits in the labelling of facial

emotional expression have been found in unaffected relatives compared to healthy control subjects [89]. Schenkel et al. found that bipolar youths had more difficulty performing social cognitive tasks that measure theory of mind (i.e., inferences of others' thoughts or intentions) compared with controls, especially in emotional contexts [90]. Whitney et al. noted significant impairments in social reciprocity in youths who have a parent with BD and presented mood dysregulation symptoms without BD. However, in this study, no difference in performance with regard to theory of mind or affect recognition was found [91]. A smaller study on the offspring of BD parents reported an association between the results on the Wisconsin Card Sorting Test and a later risk for the development of BD [43].

Neuroanatomical features

Cortical atrophy, an enlargement of the ventricles and a reduction in the grey matter volume, were noted over the course of BD [14,92-94]. However, compared to psychosis disorders, fewer structural impairments were found at an early and very early stage (e.g., prior to the onset of the first thymic episode) [93]. A progressive loss of brain grey matter in the frontal lobe was reported in a 2-year follow-up period after the first psychotic episode relative to controls [95]. Emerging data from longitudinal neuroimaging studies are beginning to elucidate abnormalities in cortical development associated with a higher risk of developing BD. For example, a reduction in the level of N-acetylaspartate, a marker of neuronal integrity, was found in the dorsolateral prefrontal cortices and hippocampi of children who are at risk of developing BD [96]. Singh et al. reported atypical patterns of prefrontal and subcortical intrinsic connectivity in the healthy offspring of parents with BD [97]. Abnormalities in amygdala development and in other regions of the limbic system (e.g., the hypothalamic nuclei) in BD were also found in structural and functional neuro-imaging

studies [98,93]. It has been suggested that such neuroanatomical changes that occurred at a very early stage of BD could partly explain the increased vulnerability to environmental stress that is observed in at-risk youths [9,14,6,12].

Limitations and further research

In recent decades, studies on biological and neuroimaging biomarkers have led to a better understanding of the physiopathological mechanisms that are involved in BD. Moreover, the lack of specificity of current risk factors and prodromal clinical symptoms strongly supports the developing of biomarkers to identify youths who have a higher risk of developing BD. Ideally, biomarkers will help to measure the accurate risk of developing BD and guide treatment in youths with non-specific symptoms (e.g., for adolescents who are referred for a first episode of depression) [99]. Encouraging findings that concern the inflammatory biomarkers at a later stage of BD have been examined in adults, but few studies have been conducted in youths. Preliminary studies should be replicated in larger samples and should use a longitudinal design to test the predictive validity of such biomarkers. Because much focus is put on the sensitivity of putative biomarkers, too little attention is paid to their specificity. For example, Mesman et al. reported that the abnormal expressions of genes that are involved in inflammation did not differ between youths who have developed a mood disorder, those who have developed a non-mood disorder, and those who have not developed any psychiatric disorder [87]. In contrast, Padmos et al. noted that monocyte gene activation, which is found in adolescent bipolar offspring, might potentially predict the development of mood disorders [86]. Moreover, the identification of one biomarker as a predictor for both BD and other psychiatric disorders, such as psychosis disorders, could also reflect the overlap

between these diseases. Further studies would be needed to assess the extent to which biomarkers are specific to BD or reflect a general vulnerability to psychiatric disorders.

(iv) Efficacy of preventive interventions

The objectives of a preventive intervention are to reduce early symptoms, enhance the ability to cope with dependent and independent stressors, and prevent or delay the onset of a disorder [100]. Psychosocial and pharmacological treatments have been proposed as preventive interventions for youths who are at risk of BD.

Psychosocial interventions

The use of psychoeducational or psychotherapeutic interventions as a first step to preventing BD has been proposed, given the favourable benefit/risk ratio and the greater level of satisfaction among young patients and their families when compared to pharmacological treatment [101]. Four studies have been conducted to evaluate the efficacy of psychosocial interventions in children who are at risk of BD [102-105]. Nadkarni and Fristad examined the effect of multi-family psycho-educational psychotherapy for 8 weeks on 17 subjects with depressive symptoms [102]. A lower conversion rate to BD spectrum disorders was observed in the treated group after a 1-year follow-up. In an open study, which was conducted in 13 children of adults with BD with subthreshold mood symptoms, an improvement in symptomatology and functioning levels after a 1-year follow-up was found in youths who received Family Focused Therapy for High Risk children (FFT-HR), in addition to their usual treatment [103]. FFT-HR was associated with a faster recovery in a controlled randomised

trial conducted in 40 subjects over 12 months [104]. Interpersonal and Social Rhythm Therapy (IPSRT), which targets altered social and sleep patterns, showed encouraging findings in a pilot study conducted on 13 youths [105]. A randomised controlled multi-centre clinical trial is being conducted to evaluate the efficacy and safety of a specific cognitive-behavioural psychotherapy (CBT) for young people who are at risk of BD [106].

Pharmacotherapy interventions

Although mood stabilisers and atypical antipsychotic medications exhibit efficacy for the curative treatment of manic episodes in adolescents [107,108], their efficacies in the treatment of prodromal mood symptoms are largely unknown. Thus far, only four studies have been conducted to evaluate their efficacy in this context [109-112]. A study on 30 youths who suffered from prepubertal major depressive disorder, with putative predictors of future BD, was performed to evaluate the efficacy of lithium. In this 6-week, double-blind, placebo-controlled trial, lithium was not found to be more efficacious than the placebo. However, the effect of lithium on the prevention of the onset of BD was not examined [109]. The effect of valproate sodium was evaluated in a 12-week open trial that included 24 children with first-degree relatives with BD and major depressive disorder, cyclothymic, dysthymic, attention-deficit/hyperactivity disorder, or other affective symptoms. Of the 23 subjects who completed the trial, 18 (78%) were considered to be “very much improved” or “much improved” [112]. A randomised, placebo-controlled study was conducted to evaluate the efficacy of valproate sodium in 56 youths who had at least one biological parent who suffered from BD, BD-NOS, or cyclothymia. After 5 years of follow-up, the treated group did not differ from the placebo group with respect to the survival time to the discontinuation of medication (the primary study outcome variable) or discontinuation due to a mood event

[110]. The effect of quetiapine has been evaluated in a 12-week open trial in 20 adolescents with first-degree relatives with BD-NOS, BD-II, dysthymia or major depressive disorder, with a response rate of approximately 87% [111]. Different authors have suggested that in the early phases, intervention should focus on non-specific neuroprotective strategies and psychosocial intervention, while considering the few potential side effects compared to lithium or antipsychotics [113,80,114,115]. McNamara et al. recommended that patients with prodromal symptoms should be treated using omega-3 fatty acids and vitamins [113]. Preclinical and clinical studies supported the positive impact of omega-3 fatty acid supplementation for reducing depressive symptom severity in children and adolescents with mood disorder [116]. Favourable effects of omega-3 fatty acid supplementation were observed in the case of bipolar depression, and manic episodes, according to a meta-analysis of five clinical trials conducted in BD patients [117]. Patients who fulfil the criteria for BD should be treated in accordance with current recommendations for manic or hypomanic episodes.

Limitations and further research

The scientific evidence that is available with regard to the effects of psychotherapeutic interventions is dramatically insufficient for meeting the needs of clinicians. The effect of interventions that target environmental risk factors (e.g., substance use) has not been properly evaluated on the future risk of developing BD [107,26,18]. The neuroprotective effect of anti-inflammatory agents must be evaluated on youths who are at risk of BD.

3. Staging models to define individual subthresholds for intervention

Different staging models

Given the consequences of a delayed intervention and the importance of long-term tolerability, models that are based on a measure of individual risk for developing BD have been proposed. Clinical staging models have been proposed as a rational method to classify patients according to their level of risk of developing BD [100,118-122,113]. They provide a framework that could help to implement a gradual approach for the interventions. For example, safe and well-tolerated interventions could be proposed at an early stage, although treatments that are more likely to be associated with adverse effects should be reserved for those who have a higher risk for transition [123]. Table 2 presents the staging models that were proposed for BD and the definition of the stages for each one. It should be noted that certain staging models, such as those developed by Berk or Kapczinski, do not specifically focus on the transition to BD and instead encompass all of the natural courses of the disease, from an early stage without specific symptoms (e.g., stage 0 in Berk's model) to a severe form (e.g., stage 4 in Berk's model) [124,6,31].

[Insert Table 2 about here]

Three staging models were specifically developed to focus on the transition from the at-risk stage to the onset of a first manic or hypomanic episode [100,120,121]. These models are based on specific scales to measure different risk factors (as illustrated in Table 1) and to detect psychopathological and functional impairments that precede the onset of BD. Corell et al. developed the “Bipolar Prodrome Symptom Scale Prospective” (BPSS-P) by

retrospectively questioning child and adolescent patients who had experienced their first manic episode [100]. Bechdolf et al. operationalised the category of “Bipolar at Risk” (BAR) by analogy to the Ultra-High-Risk criteria for psychosis [119]. Leopold et al. set up the “Early Phase Inventory for Bipolar Disorders” (*EPIbipolar*) which is based on a systematic review of the literature that concerns putative risk factors for developing BD in young adults [121]. The notions of “subclinical-attenuated” [100], “subthreshold manic symptoms” [119] and “subthreshold affective symptoms” [121] are based on findings from prospective studies that were conducted on the general population, in the offspring of patients with BD, in people with unipolar depression and in retrospective studies on BD patients. Berk et al. proposed a staging model that encompassed all of the natural history of BD, from the early, pre-risk status to severe persistent disease [124]. This model focussed more specifically on the distinct neurobiological correlates of the stages of the disorder. The description of each stage referred to not only the clinical symptoms but also the functional impairments and cognitive difficulties. This initial model was further developed by Kapczinski [6]; their work emphasised the assessment of patients in the inter-episodic period and included a latent phase and four stages.

Validity of staging models

A staging model should be able to classify patients according to their level of severity and to predict a transition to the subsequent stages. Table 3 shows the studies that were conducted to measure the validity of the staging models, in particular the predictive value (i.e., the possibility of discriminating between different levels of BD) and the reliability (i.e., the adequacy of staging between and within the raters).

[Insert Table 3 about here]

Corell et al. found a good internal validity and inter-rater reliability of the BPSS-P when applied to 205 referred youths [118]. However, no information was available on the predictive value of the BPSS-P score. Leopold et al. found 16% of youths to be at risk of BD in a referred sample [122]. The measure of the internal consistency of *EPIBipolar* was not reported in the study. Considering the cross-sectional design of the study, the transition rate of this group is not known. Bechdolf et al. followed BAR screen-positive individuals (n=35) and a matched control (n=35) over a period of 12 months [120]. The clinicians who made the diagnoses were blind to the at-risk group allocation. Five cases out of 35 made the transition to the first hypomanic/manic episode during the follow-up. The differences between the subgroups were not significant. A previous study reported a good inter-rater reliability with regard to the Comprehensive Assessment of At-Risk Mental States scale that was used to identify the at-risk youths [119]. The distinction between the different groups in the staging model proposed by Berk is supported by longitudinal studies, which have stressed the progressive increase of residual thymic symptoms, cognitive difficulties and functional impairments during the course of the disorder. Reinares et al. used latent class analysis to define the subtypes of patients with BD [125]. Two groups were identified; they differed by the episode density (the total number of episodes divided by the duration of the illness), level of residual depressive symptoms, estimated verbal intelligence and inhibitory control. Such findings support the use of both cognitive difficulties and persistent symptoms for assigning individual patients into prognostic classes in staging models. Rosa et al. compared the functional impairments and cognitive impairments that were presented by 87 referred patients according to the levels of the staging models [126]. They found a linear association between the severity of the functional impairment and the clinical stages. Moreover, the patients in

group III and group IV presented worse cognitive measures than the healthy controls. Further studies are needed to measure the transition rate from one stage to the other using longitudinal data.

Limitations and further research

Staging models must be better operationalised and validated by empirical longitudinal research. Only one study has examined the predictive value of staging models on longitudinal data [120]. Because more focus has been placed on sensitivity, few studies have discussed the problems of the specificity of the staging models. Further studies are needed to explore the possibility of pluripotent models for serious mental illness [21]; Fusar-Poli suggested that focus should be placed on a general at-risk presentation (“Ultra High-Risk”) to prevent both psychosis and non-psychosis disorders [71]. Furthermore, the role of biomarkers in increasing the predictive value of the staging models, especially at an early stage, deserves further investigation.

Conclusions

The consideration of minor symptoms as risk factors for the development of complete mental disorders and as targets for preventive interventions represents a major paradigm shift in psychiatry. The social burden of BD and the poorer prognoses in the case of delayed treatment make the development of preventive interventions essential. In this paper, the principal limitation for a preventive approach to BD in children and adolescents concerns the

lack of specificity of clinical and non-clinical markers. In particular, promising evidence with regard to the development of biomarkers exists, but it should be regarded as largely preliminary. Despite encouraging results that support the benefits of staging models in BD, the algorithms that have been developed still need to be more empirically validated in children and adolescents.

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Table 1. Risk factors for the onset and development of bipolar disorder.

First-degree relatives of patients with BD
<p>Clinical manifestations</p> <ul style="list-style-type: none"> Subsyndromal bipolar spectrum symptoms Depressive symptoms Frequent comorbid disorders (anxiety, ADHD) Change in sleep
Temperamental traits
<p>Substance use</p> <ul style="list-style-type: none"> Misuse and dependence Antidepressant use
<p>Environmental factors</p> <ul style="list-style-type: none"> Abuse and maltreatment Conflictual family

Most of the staging models are based on additive risk factors that include genetics, clinical phenotypes, personality traits, substance abuse, and environmental factors.

Table 2. Staging models developed for bipolar disorder.

Correll et al. 2007, 2014 [92,110]	Bipolar Prodrome Symptom Scale Prospective	
	Early prodromal stages	Subclinical, attenuated non-specific manic symptoms
	Late prodromal stage	BD-NOS
	A subsyndromal stage	Cyclothymia and hypomania
	Syndromal stage	BD-I/II
Bechdolf et al. 2010, 2014[111,112]	Bipolar at Risk (BAR)	
		Aged between 15- 25 years Fulfil criteria of at least one of three groups within the last 12 months Exclusion criteria: history of manic episode ≥ 4 days /psychosis ≥ 7 days; past treatment with an antipsychotic ≥ 3 weeks or a mood stabiliser ≥ 6 weeks; IQ below the normal range; organic brain disorder.
	Group 1	Sub-threshold manic symptoms: (criteria for a manic episode ≥ 2 consecutive days but < 4 days)
	Group 2	Depression plus cyclothymic features (sub-threshold manic symptoms not meeting group 1 criteria)
Leopold et al. 2012, 2014[114,113]	The Early Phase Inventory for Bipolar Disorders (EPI <i>bipolar</i>)	
		Primary risk factors (1,2) and secondary risk factors (3-7) (1) Family history of BD (2) Subthreshold affective symptoms increasing cyclothymia dynamic (hypo)manic prodrome (3) Changes in sleep and circadian rhythm (4) Substance use (5) ADHD symptoms or diagnosis (6) Impairment of psychosocial functioning (7) Symptoms of affective disorder other than BD or fearfulness/anxiety
	No risk at present	
	Risk status	Specific changes in sleep and circadian rhythm and at least one of the other secondary risk factors
	High risk status	One primary and at least one secondary risk factor
	Ultra-high risk status	More than one primary risk factor
McNamara et al. 2010 [105]	Stage I	
		Putative risk factors without prodromal symptoms First-degree relative Physical/sexual abuse Psychosocial stress Substance use/abuse Stimulant; medications N-3 fatty acid deficiency
	Stage II	Prodromal clinical features: ADHD; unipolar depression; hypomania; anger/irritability; anxiety
	Stage III	Onset of an episode of (hypo)mania
Berk et al. 2014 [116]	Stage 0	
		Increased risk of BD; no specific current symptoms
	Stage 1a	Mild or non-specific symptoms of mood disorder
	Stage 1b	Ultra-high-risk: moderate but subthreshold symptoms, with neurocognitive changes and functional decline to caseness
	Stage 2	First episode of threshold mood disorder
	Stage 3a	Recurrence of sub-threshold mood symptoms
	Stage 3c	Multiple relapses
	Stage 4	Severe, persistent illness as judged on symptoms, neurocognition and disability criteria

Kapczinski et al.
2009; Brietzke et al.
2012 [6,29]

Latent stage	Individuals at an ultra-high-risk for developing BD present mood and anxiety symptoms and increased risk (e.g., positive family history)
Stage I	Patients who have a diagnosis of BD and return to a baseline level of functioning when the episodes resolve (without cognitive impairment)
Stage II	Mild functional impairment confined to co-morbidities (rapid cycling or current axis I or II comorbidities, transient cognitive impairment)
Stage III	Severe impairment in cognition and global functioning (unable to work or very impaired performance)
Stage IV	Patients are unable to live autonomously due to BD morbidity

Table 3. Evaluation of the internal and external validity of staging models developed for bipolar disorder.

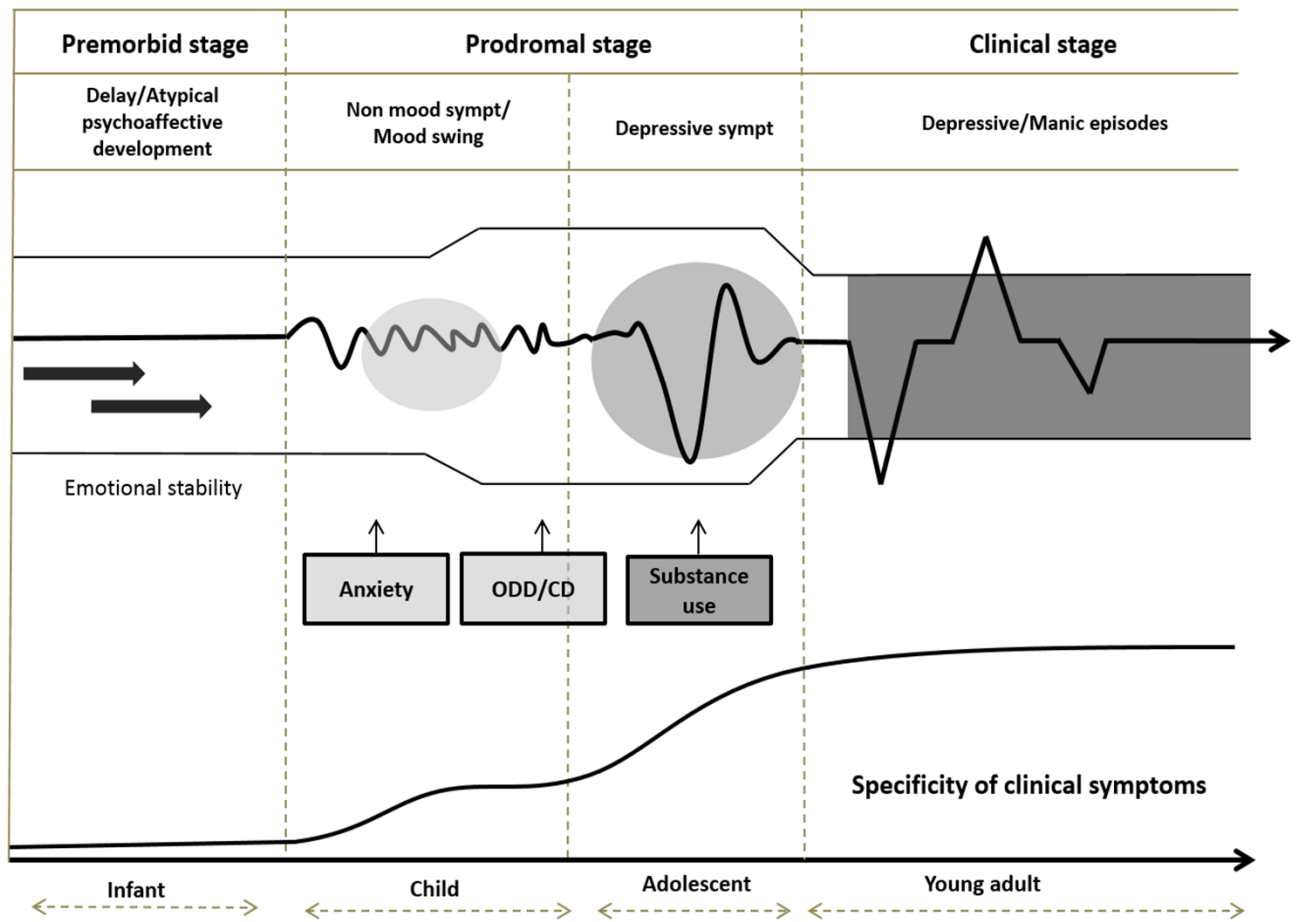
	Methods	Population	Scales	Diagnosis/Classification	Internal validity	Predictive value
Correll et al. 2014 [110]	Cross-sectional study	N=250 12-23 years old US	BPSS-P	All mood spectrum disorders n=129 (52%) Depression spectrum disorders n=77 Mood disorders NOS n=14 BD-NOS n=14 BD-I/BD-II/ Cyclothymia n=11	For General symptoms $\alpha=0.74$ ICC = 0.939 Manic symptoms $\alpha=0.87$ ICC = 0.934 Depressive symptoms $\alpha=0.89$ ICC = 0.985	No evaluation
Leopold et al. 2014 [114]	Cross-sectional study	N=180 12-40 years old Germany	EPI <i>bipolar</i> ; BPSS-P	At risk n=29 (16%)	No evaluation	No evaluation
Bechdolf et al. 2010 [111]	Retrospective study medical file audit follow-up 265 days	N=173 15-24 years old Australia	Comprehensive Assessment of At-Risk Mental States	At-risk n=22 (13%)	Classification BAR/non-BAR k=0.83	Conversion rate 22.8% OR=44.12 [4.87-400.10]
Bechdolf et al. 2014[112]	Prospective study follow-up 12 months	N=559 15-24 years old Australia	Comprehensive Assessment of At-Risk Mental States	At risk n=35 (6%) Group 1 n=10 Group 2 n=20 Group 3 n=3 Group 1+2 n=2	Classification BAR/non-BAR k=0.83	Conversion rate 14.3% Group 1n=3 Group 2 n=2 Group 3 n=0

BPSS-P= Bipolar Prodrome Symptom Interview and Scale–Prospective; ICC= intra-class

correlation; α = Cronbach's alpha; k = Cohen's Kappa

EPI*bipolar*= Early Phase Inventory for bipolar disorder

Figure 1. Developmental course of bipolar disorder.



Sympt=symptoms; The high rate of comorbid disorders during childhood, as well as the on-going development of emotion regulation skills partly explained the low level of specificity of mood symptoms at this age. In contrast, the presentation of mood disorders in adolescents is more similar to that described in adults

