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BIPOLAR DISORDER (J SOARES AND M SANCHES, SECTION EDITORS)

Prevention of Bipolar Disorder: Are We Almost There?

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Abstract

Purpose of Review A considerable portion of bipolar patients do not respond well to available therapeutic strategies. Therefore, early identification of BD and its possible prevention are of high interest. We performed a critical review of the literature, focusing on the evidence with putative implications for the prevention of BD.

Recent Findings Several psychopathological findings among individuals at high genetic risk for BD may correspond to a prodromal stage of BD. Neuroimaging alterations and other biological findings among those at high risk for BD have also been identified. However, the ability of these strategies to predict future progression to BD is limited. Similarly, available evidence does not support the preventive treatment of individuals at high risk for BD.

Summary Current research findings do not support the implementation of therapeutic interventions aiming at the prevention of BD. The therapeutic approach for symptomatic non-bipolar individuals at high genetic risk for BD is of high interest from a clinical and research standpoint.

Keywords Bipolar disorder · Offspring · Prevention · Biomarker · Neuroimaging · Treatment

Introduction

The classic concept of bipolar disorder (BD) as a condition in which periods of elated mood (mania or hypomania) alternate with depressive episodes and periods of remission has been, over the last two decades, challenged. As a matter of fact, evidence suggests that, concerning the course of BD, residual symptoms and a chronic progression seem to correspond to the rule rather than the exception [1, 2]. Not surprisingly, the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 listed Bipolar Disorder (BD) among the leading causes of disability worldwide [3]. In one study, the direct costs associated with the health care of patients with BD were estimated at US$ 7 billion/year, with indirect costs (including those resulting from absenteeism, low productivity, and the interaction with the criminal justice system) at US$ 38 billion [4]. Moreover, patients with BD appear to have 2 to 10 fold higher rates of mortality than the general population, not only due to the elevated risk of suicide but also as a result of medical conditions that seem to be particularly prevalent among these patients, such as cardiovascular diseases, diabetes, and obesity [5].

Even though available treatments for BD have expanded beyond the classic first-line mood stabilizers, such as lithium and valproic acid, the treatment response among patients with bipolar disorder, considering the currently available treatments, remains remarkably poor. Data from the STEP-BD study indicates that almost 50% of BD patients experienced recurrence over the 2-year follow-up period, whereas slightly more than half of the symptomatic participants achieved recovery [6]. Furthermore, despite the high number of ongoing clinical trials testing the efficacy of a large range of agents in the treatment of BD, none of these novel treatments will likely become available within the next several years [7].

Given the mentioned treatment limitations and prognostic implications of BD, as well as its overall impact on individuals' functioning and well-being, considerations have been made on the need for early detection and, possibly, the prevention of that condition. The present paper starts with a brief review of the evidence on populations at higher risk for the development of BD, followed by a summary of some of the interventions that may have a potential role in preventing the future development of BD in high-risk individuals. Finally, it

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addresses the perspectives in the prevention of BD from a critical point of view.

High-Risk Populations

Twin and family studies point to elevated rates of heritability in BD. Twin studies point to concordance rates for BD ranging from 40 to 70%, with a 5–10% risk of BD among first degree relatives of bipolar patients, a risk seven times higher than the one observed in the general population [8]. Since the indiscriminate implementation of strategies aiming at the prevention of BD would not be doable, and considering that, 50 to 66% of BD patients have their illness onset prior to age 18 [9], the identification of specific at-risk groups of individuals more likely to benefit from these interventions is of high interest. This is the case for offspring of bipolar parents, whose study allows not only the assessment of risk factors associated with the future development of BD among genetically vulnerable individuals but also the characterization of prodromal symptoms of BD. Such advances may ultimately make viable approaches aiming at reducing the likelihood of progression of the disease to full forms of the condition.

Psychiatric Morbidity Among Offspring of Bipolar Parents

A large amount of evidence indicates that offspring of parents with BD are at higher risk for the development of psychiatric conditions in general and mood disorders in particular. Evidence indicates that 50 to 60% of the offspring of bipolar parents seem to meet criteria for a mental disorder, particularly anxiety disorders, disruptive behavior disorders, and mood disorders [10]. An early metanalysis reported an almost three times higher risk for developing any psychiatric condition and a four times higher risk for developing mood disorders [11]. The results of cohort studies with offspring of BD parents seem to corroborate these findings, although the rates of bipolar spectrum disorders among offspring seem to vary considerably, ranging from 4.8 to 57% [12•]. Other psychiatric conditions commonly found in this population are anxiety disorders, which, in one study, were described as increasing the adjusted risk for mood disorders [13], acute depressive episodes and dysthymic–cyclothymic disorders [14], and attention and behavioral problems [15].

Prodromal Symptoms and Clinical Predictors of Future Conversion to Bipolar Disorder

Evidence suggests that more than 50% of high-risk individuals who developed BD experience prodromal symptoms (characterized as symptoms that precede the manic or hypomanic index) prior to age 14 [16]. These prodromal symptoms may be non-specific, although some of them are more strongly correlated with future conversion to BD, including mood lability, depressive episodes [17], anxiety, sleep disturbances, conduct disorder, and attentional impairment [16]. Subthreshold manic/hypomanic symptoms seem to be a strong predictor of BD conversion [18]. In a metanalysis [19], the duration of prodromal symptoms in BD was found to be, as a rule, prolonged, ranging from 4.6 to 130 months. The same metanalysis pointed to significant heterogeneity in bipolar prodromal symptoms, with a strong correlation between prodromal symptoms and subsequent mood polarity.

Moreover, the nosological value of a diagnosis of BD NOS (not otherwise specified) as prodromal state for BD I or II has been object of great interest. It is known that this diagnosis, particularly in youth, is highly unstable, with rates of conversion to BD I or II ranging from 29 to more than 50% [20, 21•]. In a 2018 paper, Birmaher et al. [21•] described the validation of a risk calculator, able to predict conversion from BD NOS to BD I or II over a 5-year period. The authors utilized data from two longitudinal studies with at-risk populations, the Pittsburgh Bipolar Offspring study [22] and the Course and Outcome of Bipolar Youth (COBY) study [23]. In the COBY sample, the calculator was able to predict conversion to BD with an area under the curve of 0.71, indicating good discrimination between converters and non-converters. Risk for conversion was higher among youngsters with increased manic symptoms, depressive symptoms, anxiety, mood lability, and family history of mania.

Moreover, questions have been raised about the differences in prodromal symptoms in BD versus schizophrenia spectrum disorders. A recent study reported considerable overlap between the prodromal features of both conditions, with three or more subsyndromal manic symptoms and ADHD showing more specificity for later development of BD, whereas brief limited intermittent psychotic symptoms were stronger associated with late development of schizophrenia spectrum disorders [24]. Another group [25] recently described the development and validation of a scale specifically designed to assess BD prodromal symptoms, the Bipolar Prodrome Symptom Scale-Abbreviated Screen for Patients (BPSS-AS-P). The instrument in question was found to have good discriminant validity and, of notice, was not correlated with instruments measuring positive and negative symptoms in psychotic conditions.

Finally, in a recent task force report from the International Society of Bipolar Disorders, based on the critical analysis of retrospective and longitudinal studies, several clinical features were listed as clinical precursors of BD (Faedda et al., 2019). Those include cyclothymic features, attenuated manic symptoms, subthreshold hypomanic symptoms, recurrent depression, panic anxiety, psychotic features, and positive family history of BD. The report emphasized, however, that the predictive value of any risk factor continues to be basically unknown, in light of available evidence.

Neuroimaging and Biological Predictors of Future Bipolar Disorder

Despite the conflicting results regarding the search for biomarkers in BD, the characterization of neuroimaging findings associated with progression to BD among high-risk individuals remains of high interest and would help in the identification and selection of individuals more likely to benefit from interventions aiming at preventing the development of BD.

Anatomical neuroimaging studies of brain areas involved in emotional regulation among offspring of BD patients have produced mostly negative results [26•]. Some sporadic findings include decreased gray matter in the hippocampal/parahippocampal gyrus [27]; cortical thinning in temporal, frontal, and supramarginal areas [28]; enlarged amygdala [29]; and decreased gray matter volume in the right inferior orbitofrontal, right middle frontal, and bilateral superior and middle temporal regions [30]. In a machine-learning study, white matter structure (especially in the inferior/middle frontal gyrus, inferior/middle temporal gyrus, and precuneus) was able to provide good discrimination between high-risk BD offspring and controls [31]. Finally, in a recent study with BD offspring, a statistically significant association between familial risk and reduced nucleus accumbens volume was identified [32]. Furthermore, functional MRI studies point to task-related abnormalities in the prefrontal-subcortical and prefrontal-amygdala circuit in offspring of BD patients [26•]. In a functional MRI study, BD offspring displayed abnormal activation patterns associated with a reward-processing task [33]. Finally, abnormal brain connectivity in BD offspring has also been identified through resting state fMRI studies, particularly in the ventrolateral prefrontal cortex and in the striatal-thalamus circuit [34, 35].

Although some of the findings above may be interpreted as possible markers of vulnerability to BD, evidence is even scanter when it comes to predicting future bipolar conversion. In a recent study utilizing data from the Pittsburgh Bipolar Offspring Study (BIOS), researchers attempted to identify neuroimaging patterns longitudinally associated with certain mood dimensions 29 months later [36]. Some findings, including lower bilateral parietal cortical thickness, greater left ventrolateral prefrontal cortex thickness, and lower right transverse temporal cortex thickness, were correlated with future higher mixed/mania factor scores. On the other hand, lower bilateral parietal cortical thickness, greater right entorhinal cortical thickness, and greater right fusiform gyrus activity during emotional face processing were found to be associated with higher irritability factor scores.

In a 2014 meta-analysis of mixed cognitive and emotional activities among high-risk adolescents, pediatric bipolar patients, and controls, the bipolar offspring displayed greater activity in the right DLPFC, insula, and left cerebellum compared to patients with bipolar patients. The latter, when compared to HC, were found to have higher activation in the right amygdala, parahippocampal gyrus, medial PFC, left ventral striatum, and cerebellum, as well as lower activation in the right VLPFC and the DLPFC [37]. It was hypothesized that the hyperactivation in unaffected bipolar offspring was secondary to greater compensatory deployment, which seems to be absent in bipolar patients. This hypothesis is partially in agreement with contemporary neurofunctional models according to which BD results from increased activity of limbic areas associated with decreased regulatory activity from frontoparietal structures [38].

Similarly, in a recent review paper, Frangou [26•] proposed that certain functional patterns in the brain circuits involved in different emotional and cognitive domains were associated with either disease expression or resilience individuals genetically predisposed to BD. The model in question was conceptualized according to available functional neuroimaging among bipolar patients and at risk individuals. For example, with respect to impaired interference control, disease expression was associated with decreased activation in the ventrolateral prefrontal cortex and caudate, as well as decreased connectivity between both structures. Regarding the impaired working memory domain, disease expression was associated with decreased connectivity within the white matter network and hypoactivation of the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex. Considering the facial recognition domain, disease expression was associated with increased activation of limbic regions and decreased activation of the dorsolateral prefrontal cortex. Other abnormalities in functional connectivity associated with disease expression include increased intra-network connectivity of the secondary motor and somatosensory regions, as well as increased network cohesion and reduced inter-network integration of anterior default mood network regions [26•].

With respect to other biological markers, studies looking into peripheral biomarkers among offspring of BD patients have been largely negative [39]. According to prospective data from the Dutch bipolar offspring study [40], bipolar offspring were found to have increased inflammatory gene expression in monocytes, as well as increased serum PTX3 levels and decreased BDNF levels during adolescence. These findings, although supporting the proposed role of inflammation as a marker of vulnerability to BD, did not seem to have predictive value as for the future development of a mood disorder.

Interventions for the Prevention of BD

Since, based on available evidence, it is not possible yet to determine which individuals (among those with high genetic risk for BD) will effectively develop the disease, the implementation of therapeutic strategies aiming at preventing future

conversion to BD is highly challenging and carries several technical and ethical implications. A proposed approach is, when applicable, to focus on symptoms instead of diagnosis, while at the same time carefully balancing the risks and benefits of therapeutic interventions (especially medications) that potentially could precipitate a manic or hypomanic state and, paradoxically, accelerate the progression to BD among susceptible individuals.

Pharmacological Interventions

In one of the few studies assessing the efficacy of pharmacological interventions in non-bipolar offspring of bipolar parents, Chang et al. [41] analyzed the impact of treatment with divalproex on young bipolar offspring (24 children and adolescents) with mild to moderate mood symptoms. Participants met criteria for different psychiatric conditions, including major depressive disorder, dysthymic disorder, cyclothymic disorder, and attention-deficit/hyperactivity disorder, but not BD. The authors reported a response rate of 78% according to the CGI. The open-label design of the study and the absence of a control group limit the generalization of the findings. In another study [42], 18 bipolar offspring who met criteria for bipolar disorder not otherwise specified or cyclothymic disorder, were treated with divalproex in a double-blind, placebo-controlled trial. No statistically significant differences were found between groups with respect to improvements in mood symptomatology. A third study [43] described positive effects of quetiapine in the treatment of bipolar offspring. Although none of the subjects met criteria for BD I, they did meet criteria for other conditions, including BD not otherwise specified, BD II disorder, major depressive disorder, dysthymic disorder, and cyclothymic disorder.

With respect to nutritional supplements, Sharpley et al. [44] examined the possible role of folic acid supplementation in the prevention of conversion to a mood disorder among individuals at high genetic risk for mood disorders, in a double-blind, place-controlled trial, over a 36-month follow-up period. Results were basically negative, with similar rates of conversion in both groups. Similarly, although not focusing specifically on BD offspring, the North America, Europe, Australia Prodrome (NEURAPRO) study examined the impact of supplementation with omega-3 unsaturated fatty acid over a 6-month period on future development of psychosis in an ultra-high risk population [45]. Results were basically negative, with no differences between the treatment groups with respect to the rates of conversion to psychotic disorders.

Overall, considering the long-term implications and potential side effects associated with treatment with antipsychotics and mood stabilizers, there is not enough evidence available to support their routine use among individuals at high risk for the development of BD who do not yet meet criteria for that condition. On the other hand, the use of antidepressants and stimulants in the treatment of this population during the prodromal phase should be carefully balanced, given the risk of precipitation of a manic episode associated with these agents. Finally, given the strong correlation between BD not otherwise specified and future development of BD I or II, high-risk individuals who meet criteria for that condition should be formally treated as bipolar patients, unless contrary evidence becomes available [39].

Psychosocial Interventions

Despite the evidence supporting the role of different psychotherapeutic interventions in the treatment of BD and their possible higher efficacy in earlier phases of the disease, intervention studies in high-risk non-bipolar individuals are scant. For instance, in a randomized study, Miklowitz et al. [46] analyzed the use of family-focused therapy, an intervention that combines psychoeducation and problem-solving skills training in the treatment of first degree relatives of bipolar patients. Participants met criteria for BD not otherwise specified, major depressive disorder, or cyclothymic disorder. Results indicated positive effects with respect to improvement and stability of mood symptomatology over a one-year follow-up, but no data yet with respect to a possible impact on the rates of conversion to BD I or II.

In another study, the effect of psychoeducational psychotherapy on patients with depressive spectrum disorders and transient manic symptoms over an 18-month period was analyzed [47]. The authors described significantly lower rates of conversion to a bipolar spectrum disorder diagnosis among participants who underwent psychoeducational therapy compared to those on a 1-year waiting list.

Finally, in a third study, the possible role of Interpersonal and Social Rhythm Therapy in the management of adolescents at high genetic risk for BD was assessed [48]. This was a pilot study with 13 subjects and, on average, participants attended half of the initially proposed 12 sessions, delivered over a 6-month period. Despite the high levels of satisfaction associated with the proposed intervention and its positive effects on certain sleep/circadian patterns, there were no statistically significant effects on mood, although the authors do state that no patients developed manic or hypomanic episodes during the observation period. The small sample size, the absence of a control group, and the short follow-up period did not properly allow the assessment of the impact of the intervention on conversion rates.

Overall, even though psychotherapeutic/psychosocial approaches might be regarded as promising early interventions for BD, additional research is necessary in order to better characterize the actual impact they can have in high-risk individuals and their effective role in preventing conversion to BD in this population. It is not clear either, based on available evidence, whether or not certain therapeutic modalities are

superior to others in the treatment of individuals at high genetic risk for BD.

Conclusions

In summary, currently available evidence does not yet allow the systematic formulation of therapeutic intervention aiming at the prevention of BD. On the other hand, the existence of a prodromal stage of BD is supported by the available literature, and the therapeutic approach for symptomatic individuals at high genetic risk who do not yet meet full criteria for BD is of high clinical relevance. The risks of long-term use of medications as well as considerations regarding the risk of medication-triggered manic or hypomanic states and conversion to BD need to be carefully balanced. Psychotherapeutic approaches are promising in the management of this population, but their actual role and benefit are not yet well established.

With respect to the search for biomarkers of future bipolar conversion, functional neuroimaging studies do support the existence of abnormalities in the brain circuits associated with the processing of emotions among high-risk individuals but are not yet able to provide guidance as for the identification of individuals more likely to develop BD in the future.

As several longitudinal studies involving individuals at high genetic risk for BD are currently in progress, the next several years should bring about a large amount of evidence regarding the factors associated with future development of BD, not only from a biological but also from a clinical standpoint. Machine learning approaches and the utilization of algorithms including imaging, behavioral, and neuropsychological data should shed some light on our current ability to predict BD, allowing a better balancing of the risks and benefits associated with the implementation of early treatment for high-risk individuals. Considering the elevated burden associated with this condition, the better characterization of individuals who could potentially benefit from early interventions corresponds to a critical need of contemporary psychiatry.

Compliance with Ethical Standards

Conflict of Interest Dr. Sanches has nothing to disclose. Dr. Soares reports research support from Allergan, Alkermes, Bristol Myers Squibb, Compass Pathways, Elan, Forest, Merck, Johnson & Johnson, membership at the Abbott and Sanofi speakers bureau, and consultancy for Astellas, outside the submitted work.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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