Prevention of Pediatric Bipolar Disorder

Integration of Neurobiological and Psychosocial Processes

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ABSTRACT: Bipolar disorder (BD) is a prevalent condition in the United States that typically begins before the age of 18 years and is being increasingly recognized in children and adolescents. Despite great efforts in discovering more effective treatments for BD, it remains a difficult-to-treat condition with high morbidity and mortality. Therefore, it appears prudent to focus energies into developing interventions designed to prevent individuals from ever fully developing BD. Such interventions early in the development of the illness might prevent inappropriate interventions that may worsen or hasten development of BD, delay the onset of first manic episode, and/or prevent development of full BD. Studies of populations at high-risk for BD development have indicated that children with strong family histories of BD, who are themselves experiencing symptoms of attention-deficit/hyperactive disorder (ADHD) and/or depression or have early mood dysregulation, may be experiencing prodromal states of BD. Understanding the neurobiological and genetic underpinnings that create risk for BD development would help with more accurate identification of this prodromal population, which could then lead to suitable preventative interventions. Such interventions could be pharmacologic or psychosocial in nature. Reductions in stress and increases in coping abilities through psychosocial interventions could decrease the chance of a future manic episode. Similarly, psychotropic medications may decrease negative sequelae of stress and have potential for neuroprotective and neurogenic effects that may contribute to prevention of fully expressed BD. Further research into the biologic and environmental mechanisms of BD development as well as controlled early intervention studies are needed to ameliorate this significant public health problem.

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INTRODUCTION

Bipolar disorder (BD) affects up to 4% of the U.S. population\(^1\) and leads to costs of more than $45 billion per year.\(^2\) A total of 25–50% of individuals with BD attempt suicide at least once, and 8.6–18.9% die by suicide.\(^3\) Suicidal risk appears highest in childhood-onset BD,\(^4\) with nearly one-third of children and adolescents with BD already having had a suicide attempt.\(^5\) Between 15% and 28% of bipolar adults experience illness onset before the age of 13 years, and between 50% and 66% before the age of 19 years.\(^6\)-\(^8\) The exact prevalence in children is unknown, but estimates range from 420,000–2,072,000 among U.S. children alone.\(^9\) Onset of BD in childhood or adolescence confers a more severe, adverse, and continuously cycling course of illness than adult-onset, typically with more mixed episodes, psychosis, and comorbid disorders.\(^10\) The complexity of early-onset BD, especially given high rates of comorbidity with attention-deficit/hyperactive disorder (ADHD), conduct disorder, anxiety disorders, and substance abuse, usually makes these patients more treatment-refractory than adults with BD.\(^8,11,12\) Thus, pediatric-onset BD patients are often severely derailed in social, academic, and emotional development.

In the last decade, much research has gone into discovering effective pharmaco- and psychotherapies to treat BD in children and adults. However, despite these efforts, BD remains difficult to treat. Furthermore, morbidity and mortality have not appreciably improved over the last 20 years,\(^13,14\) which likely reflects the chronic disabling nature of the disorder and the fact that other than lithium, medications used to treat this disorder have all originally been developed to treat other conditions. Therefore, it appears prudent to focus energies into developing interventions designed to prevent individuals from ever fully developing BD. Such interventions early in the development of the illness might prevent inappropriate interventions that may worsen or hasten development of BD, delay the onset of first manic episode, and/or prevent development of full BD.

IDENTIFICATION OF PRODROMAL PEDIATRIC BD

Before intervention studies can take place, methods for detecting a suitable high-risk population must be determined. It is clear that a family history of BD elevates risk for BD.\(^15\) As twin and family studies report a 59-87% heritability of BD, first-degree relatives of probands with BD are at very high risk of BD themselves.\(^16\) Therefore, these relatives are a good starting point for identifying children and adolescents at high-risk for BD development.
High-Risk Studies

Children of parents with BD (bipolar offspring) are a logical population in which to implement preventative interventions. A meta-analysis of studies conducted before 1997 found that offspring of parents with BD were at 2.7 times higher risk for development of any psychiatric disorder and 4 times higher risk for developing a mood disorder than children of parents without psychiatric illness. Recent studies have found that 50–60% of such offspring have some type of psychiatric disorder, especially mood, anxiety, and disruptive behavior disorders. Rates of BD spectrum disorders in these offspring range from 14–50%, and rates of major depressive disorder (MDD) range from 7 to 43%.

Putative Prodromal BD

Symptom complexes predating the first manic episode can be identified from studies of high-risk samples. The high rate of MDD in bipolar offspring raises the distinct possibility that those children are experiencing an initial bipolar depression, and will experience a manic episode in the near future. In fact, the most reliable symptom complex predating mania has been depression. In a cohort of 642 adults with BD onset before the age of 18 years, approximately 60% reported depression as their initial mood episode. Prospective studies have found high rates (20–30%) of switching to mania in children who initially presented with prepubertal MDD. The rate of conversion to BD in depressed children who are offspring of bipolar parents is even greater. In a 5-year prospective study of 129 children of bipolar parents, 12 of the 13 offspring who developed BD had an antecedent depressive episode.

ADHD in bipolar offspring also may be a harbinger of later BD development. In recent cross-sectional studies, approximately 27% of bipolar offspring have met criteria for ADHD or significant behavioral or attention problems. This finding, combined with the high comorbidity of ADHD and BD in childhood, family studies, and retrospective histories of ADHD predating BD onset supports that ADHD in certain children with strong family histories of BD is a first sign of developing BD.

Given the above epidemiological and phenomenological data, it appears that children with ADHD and/or depression who have strong family histories of BD are at high risk for BD development. The few longitudinal studies published also have supported this hypothesis. However, it is also likely that not all these children will develop full BD, and that some may never progress to this point. Therefore, diagnostic tools other than symptom complexes and family history would be helpful in diagnosing BD before mania onset. The most logical tools to pursue currently are neurobiological and genetic markers of the disorder.
NEUROBIOLOGICAL MARKERS

Despite this profile of BD prodromes in children, it is far from certain at what rates these children will develop full BD. Furthermore, by the time children present with such symptomatology, it may be relatively late in illness development for ideal intervention as a preventative measure. Therefore, other diagnostic tools, such as biological markers, would be helpful in identifying children at highest risk for BD. Neurobiological markers are a logical choice, but currently there are no neurobiological findings that are pathognomonic of BD. Identification of the brain characteristics most highly associated with BD development, along with the genetic factors that affect their development, could lead to early identification of those at highest risk for BD development and a better understanding of the pathophysiology of BD.

Neuroimaging studies in adults and children with BD have implicated numerous regions of the brain in the pathophysiology of BD, namely regions serving prefrontal-limbic circuitry. Prefrontal areas include dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (including anterior cingulate cortex), and ventrolateral (or orbitofrontal) cortex. Subcortical areas include hippocampus, caudate, putamen, thalamus, and amygdala. The amygdala is particularly interesting due to its role in mood and emotion, and consistent findings of decreased amygdalar volume in children with BD. However, this finding is not specific to BD and currently cannot be used diagnostically. Nonetheless, prefrontal amygdalar circuits are good candidates for further study in this regard. Other potential tools for marker discovery include magnetic resonance spectroscopy (MRS), fMRI, and diffusion tensor imaging (DTI).

GENETIC MARKERS

Genetic markers may also serve to help determine risk for BD as well as age at onset (AAO). It is becoming increasingly clear that BD is a polygenic disorder, with many genetic polymorphisms creating small risk for BD individually, presenting together to generate increased risk for BD. These polymorphisms could be used to help quantify risk for BD development.

For example, two potential BD gene candidates code for the serotonin transporter (5-HTT) and for brain-derived neurotrophic growth factor (BDNF). Polymorphisms of these genes have been associated with depression and BD (including early-onset and rapid-cycling varieties). However, because these polymorphisms are relatively common in the population, they likely have gross overarching effects on the brain (such as general changes in serotonergic transmission, or varied availability of BDNF), thus creating only small risk for BD by themselves. However, by a summation of various at-risk genes, it is possible that a certain level of quantification for genetic risk of BD can be achieved.
Nonetheless, it is the proteins coded by the genes, which then influence brain functioning, that are relevant to understanding how risk leads to disorder. Thus, it is useful to study the effect of genes on brain structure and function, both in “healthy” individuals as well as those with BD.\textsuperscript{54} For example, subjects with compared to those without the short allele of the 5-HTT gene have been found to have increased amygdalar and orbitofrontal activation when watching fearful faces or aversive pictures.\textsuperscript{55,56} This finding is interesting in light of the amygdalar abnormalities found in BD, including amygdalar overactivity,\textsuperscript{44,57,58} and the association of the short allele with BD.\textsuperscript{51}

Finally, AAO genes could also be used to determine risk for early-onset BD specifically. While there has been some progress in this direction,\textsuperscript{59} more research is needed. One promising area of research remaining is the possibility of trinucleotide repeat expansion in AAO regions of the chromosome, leading to anticipation of the disorder.\textsuperscript{60} Discovery of such phenomena would again help elucidate the degree of urgency needed for intervention in at-risk youth.

**EARLY INTERVENTION/NEUROPROTECTION**

First applied to seizure disorders, the theory of kindling in affective disorder holds that the combination of psychosocial stress and genetic vulnerability gradually leads to a full mood episode, after which it becomes progressively “easier” to trigger subsequent episodes, until they become spontaneous.\textsuperscript{61} Interventions early in the course of kindling may reverse the illness course. For example, rats given repeated subseizure level electrical stimulation to their amygdalae will eventually develop seizures, leading to a spontaneous seizure disorder. However, if the same rat is administered valproate prior to the onset of electrical stimulation, no seizure disorder develops.\textsuperscript{62} Thus, if similar interventions are performed early enough in bipolar illness development, it is possible that the full expression of BD could be completely averted.

**Medications**

Thus, medications have the potential to prevent BD due to antikindling effects. Another mechanism by which they might act is to stimulate healthy neurogenesis. For example, it is becoming clearer that areas in the prefrontal cortex, as well as other limbic areas, suffer neurodegeneration with prolonged bipolar illness.\textsuperscript{63–66} Stress from repeated mood episodes has been postulated to be causal to this process\textsuperscript{67,68} leading to less prefrontal mood regulation and greater cycling and treatment resistance.\textsuperscript{43} Thus, an intervention that prevents this process or restores healthy neuronal circuits in these regions could have a combined effect on preserving prefrontal function and neuronal integrity and thus prevent or delay future mood episodes.
Mood stabilizers, and to some degree antipsychotics, which are used to treat BD, have been found to have neuroprotective and neurogenic properties. Antikindling (seizure prophylaxis) properties have been described in animals with valproate and lamotrigine. Other animal studies have indicated that both valproate and lithium increase brain bcl2 (a neuroprotective protein), and activate protein kinases, which lead to increased neural dendritic growth. In humans, lithium may increase gray matter volume, and exposure to lithium or valproate may prevent decreased gray matter volumes in anterior cingulate or amygdala. Both lamotrigine and olanzapine have been reported to lead to increases in prefrontal N-acetylaspartate, a marker of neuronal density and viability.

Because of these properties, mood stabilizers and antipsychotics may prove to be effective medications in early intervention/prevention schemas. In one study, valproate was found effective in treating acute mood symptoms in children with subsyndromal BD, considered a group at high risk for BD development. Quetiapine was also effective in treating mood symptoms in a similar population, with some evidence of prefrontal N-acetyl aspartate (NAA) increase as well. However, no longitudinal studies have been conducted to investigate prevention of the occurrence of full mania with these types of agents. Clearly, while difficult to conduct, this type of study is paramount for discovering valid options for BD prevention.

**Psychotherapy**

Psychosocial stressors such as dysfunctional family environments, stressful life events, and ineffective coping strategies interact with genetic predispositions to induce the full expression of BD. The mechanisms by which environmental threats affect the course of BD may involve psychological vulnerability factors (e.g., negative cognitive styles or activation of brain circuitry involved in emotional self-regulation). Specific psychotherapeutic interventions targeted at psychosocial risk factors in high-risk individuals may help prevent or delay the onset of BD.

Although requiring more time and effort than psychopharmacology, psychotherapy can be a precise, targeted intervention with sustained effects even after it is completed. Furthermore, whereas treatment with medication may be accompanied by deleterious side effects and cannot specifically treat psychosocial stressors, psychotherapy is a safe modality that can address specific stressors and correct behaviors that lead to mood episodes, such as irregular sleep patterns or medication nonadherence.

Specific psychotherapeutic interventions for high-risk individuals should ameliorate psychosocial vulnerability factors and enhance the at-risk person’s coping ability to prevent or delay the onset of BD. Recent research has suggested that family environments characterized by high expressed emotion (EE)
attitudes\textsuperscript{84} or low maternal warmth\textsuperscript{85} are associated with poorer outcomes of pediatric BD over 2–4 year follow-ups. In a sample of children of mothers with BD, maternal negativity contributed to risk for offspring BD development through its association with impaired frontal lobe functioning as measured by the Wisconsin Card Sorting Task.\textsuperscript{86} Thus, maternal relationships in the context of family environment is one area to target for BD prevention.

Other strategies for reducing the likelihood of developing full BD can be inferred from data supporting the efficacy of psychosocial interventions for the prevention of relapse of mood episodes in patients already with BD.\textsuperscript{84} It is currently recommended that patients with BD receive both medication and adjunct psychotherapy.\textsuperscript{87,88} Thus, although extensive advances have been made in the pharmacological treatment of BD, it has become apparent that medication alone is not enough for the management of this chronic, recurrent illness. Medication noncompliance, lack of ability to recognize symptom exacerbation, and the inability to cope with stressors that precipitate illness episodes are problematic for many individuals with BD and are often related to illness relapse.\textsuperscript{89,90}

Thus, potential psychotherapeutic interventions geared toward prevention of worsening to full BD could be based on current techniques geared toward prevention of mood episode relapse in patients already with full BD. Family focused therapy (FFT) has been found effective for adolescents with BD,\textsuperscript{91} and would be a good candidate for modification for a high-risk population. Other promising candidates would be cognitive behavioral therapy (CBT)-type therapies\textsuperscript{92} or more behaviorally oriented therapies for younger children,\textsuperscript{93} both found useful in pediatric BD. Due to the highly familial nature of the disorder, a unique factor of these therapies could be the treatment of family members with BD-spectrum disorders, thus decreasing EE and stress in the family and theoretically decreasing BD risk in the at-risk family member(s). Such controlled studies in at-risk populations are clearly warranted.

\section*{CONCLUSIONS}

It is the hope that a combination of brain and genetic markers, symptom complexes, and family history can lead to more accurate diagnoses of prodromal BD. Then early intervention could occur in a population at clear, perhaps even quantifiable, risk for BD development. Promising areas for further exploration of brain markers for this purpose include prefrontal-limbic areas, especially the amygdala. However, more understanding about how alterations in the relevant circuitry lead to bipolar symptoms would likely reveal markers more specific to BD than morphometric or neurochemical abnormalities by themselves. Furthermore, the neurobiological underpinnings of circadian rhythm disruption, fairly specific to BD, are vastly understudied. The search for AAO genes as well as additional genes that are linked to BD will help the
early identification/prevention cause. Early-onset cohorts particularly should be studied to generate these candidate genes for prevention purposes.\textsuperscript{94}

Intervention studies should not wait until these markers are definitively established, as the burden of BD is too great.\textsuperscript{9} The neuroprotective and neurogenic properties of psychotropic medications are exciting; in the future the grim sentence of lifelong medications for patients with BD may be lifted if intervention with these agents, along with appropriate psychotherapies, is instituted early enough in the disorder evolution to halt the kindling process. A short, corrective course of these medications at the “right” time could also prevent prolonged exposure to them later in life. Controlled, long-term intervention studies in high-risk populations should therefore include biological and genetic assessment to more precisely match intervention with underlying neurobiology and genetic predisposition and to study effects of these interventions on brain function. Implementing psychotherapeutic and psychopharmacologic interventions that are placed upon such a neurobiological and genetic framework would be a powerful step toward the eventual eradication of this disorder.

REFERENCES


