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Treatment of psychiatric symptoms among offspring of parents with bipolar disorder

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Abstract

Purpose of Review—Bipolar disorder is highly familial and has a protracted and diagnostically confusing prodrome. This review critically evaluates recently published literature relevant to the treatment of psychiatric symptoms in high-risk offspring of parents with Bipolar Disorder.

Recent Findings—Non-pharmacological treatment options including psychotherapy, resilience promotion through good sleep, diet, and exercise hygiene, and omega-3 fatty acid supplementation are important first line interventions for high-risk offspring. There has been some success in treating this population with open-label trials with mood stabilizers and atypical antipsychotics; however, these results have not been replicated in randomized controlled trails.

Summary—Despite some progress in early identification of symptoms in offspring of parents with Bipolar Disorder, there is scarce evidence supporting the treatment of these high-risk youth to prevent psychiatric symptoms from progressing to threshold bipolar or other psychiatric disorders. There is a need for prospective and randomized trials and research that identifies reliable biomarkers to individualize treatments for these youth.

Keywords

Risk; bipolar disorder; depression; anxiety; treatment; prevention

INTRODUCTION

Bipolar disorder is highly familial, with heritability rates estimated to be as high as 85–89% [1]. This familial risk places youth offspring of parents with Bipolar Disorder at a high risk for developing a major mood disorder compared to the general population. Family studies show that compared to youth without any family history of Bipolar Disorder, youth at high-risk for Bipolar Disorder have elevated rates of mood disorders, such as major depressive disorder and Bipolar Disorder as well as other psychiatric disorders, such as anxiety and disruptive behavioral disorders [2]. These high-risk youth also have relatively more impaired psychosocial functioning, require more psychiatric treatment, have higher rates of placement

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DISCLOSURES

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in special education classes [3], display poor social skills, and exhibit poor peer social networks including attachment difficulties in infancy. Early age at onset is a poor prognostic factor for the severity and duration of depressive episodes in adulthood as well further complicated by serious morbidity, comorbidity, and suicidality throughout the entire course of illness. An inaccurate diagnosis or a delay in making the diagnosis of Bipolar Disorder can delay the onset of treatment and can increase frequency and severity of mood episodes. Indeed, a Bipolar Disorder diagnosis in childhood or adolescence can be difficult to make due to overlapping symptoms of other childhood psychiatric disorders including attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, depression and anxiety[4]. Moreover, changes in hormone levels and brain development during adolescence can lead to confusing and exacerbated mood symptom presentations due to major changes in the neural systems at this age that subserve higher cognitive functions, reasoning and interpersonal interactions, motivation as well as risk vs reward appraisal [5].

Nevertheless, the strongest risk factor for developing mania appears to be a family history of Bipolar Disorder [6].

Offspring of a parent with Bipolar Disorder may be at high risk for concordantly developing Bipolar Disorder or similar diagnoses as their parents (equifinality), or they may be at risk for developing a broad spectrum of problems (multifinality) [7,8]. For example, some at risk youth may be resilient and never experience a psychiatric diagnosis, while others may experience a range of mood and other psychiatric disorders that at some point warrant treatment. Among the most common [9] but challenging (from a treatment perspective) early-onset presentations is when an offspring of a parent with Bipolar Disorder presents with depressive symptoms. Indeed, depressed offspring of a parent with Bipolar Disorder have been found to have more severe forms of depression, including atypical depressive symptoms, and are more likely to have subsyndromal mixed manic symptoms than depressed offspring of parents with no Bipolar Disorder [10]. Many individuals with Bipolar Disorder on average wait up to 10 years or more to receive a correct diagnosis and a depression diagnosis can contribute to a longer delay in conversion [11]; early identification and treatment for individuals at risk for Bipolar Disorder may be critical. For example, improvement in specific symptoms of depression such as low self-esteem, loss of energy, and psychomotor retardation, if identified and treated early, could predict subsequent durable recovery from bipolar depression and reduce risk for subsequent affective switching [12]. Determining which symptoms to target and when to start treatment become central questions in efforts to prevent the onset of mania.

Rates of conversion to mania are variable among youth at risk for Bipolar Disorder, but are generally higher than youth without any family history of Bipolar Disorder. In a meta-analysis conducted in 1997, conversion rates to Bipolar Disorder ranged between 4% and 15% in offspring of parents with Bipolar Disorder versus between 0% and 2% in offspring of healthy parents [13]. However, this analysis does not include many others conducted in the recent years. In another study of high-risk offspring, aged 6–18 years old (n=391), compared with community offspring, high-risk offspring had significantly higher rates of subthreshold mania or hypomania (13.3% compared with 1.2%), manic, mixed, or hypomanic episodes (9.2% compared with 0.8%), and major depressive episodes (32.0%

compared with 14.9%) [14]. There also appears to be a dose related familial effect, such that having both parents with Bipolar Disorder may increase chances of Bipolar Disorder or result in a different phenotype in their offspring compared to having a single parent with Bipolar Disorder [14]. Indeed, a risk for Bipolar Disorder and other psychiatric disorders in youth offspring of Bipolar Disorder has been well demonstrated in family studies conducted around the world [2,15,16]. Exciting recent efforts have developed models of risk for converting to Bipolar Disorder among youth at familial risk for Bipolar Disorder using risk calculators [17], which may be useful to clinicians to inform frequency of monitoring and treatment options.

Rates of ADHD and anxiety are notably high among youth offspring of parents with Bipolar Disorder. Some symptoms of ADHD overlap and/or co-occur with Bipolar Disorder, which can lead to diagnostic confusion [18], especially in childhood. Duffy et al. investigated the nature of the association between anxiety and mood disorders in a prospectively studied high-risk cohort (offspring of parent with Bipolar Disorder disorder) [19]. Participants were aged 8–25 years and the control group consisted of offspring from families with no history of psychiatric illness in the parent. The cumulative incidence of anxiety disorders was higher (23.40% vs. 10.42%; HR=2.136; p=.04) and occurred earlier (9.8 vs. 14.8 years; p=.01) in high-risk youth compared to control offspring. The most common disorder in the former group was generalized anxiety disorders followed by social phobia. High emotionality (HR 1.11; p=.01) and shyness (HR 1.14; p=.005) increased the risk of anxiety disorders. Having an anxiety disorder increased the adjusted risk of mood disorder (HR 2.17; p=.0004), on average 8.5 years later (SD 6.0), although most of the high-risk offspring had a diagnosis of major depressive disorder. Other potential risk factors for developing Bipolar Disorder included physical/sexual abuse and other psychosocial stressors, substance use disorders, antidepressant medication exposure, and omega-3 fatty acid deficiency.

The type and polarity of the prodromal symptoms often matches the next episode, which may help to guide personalized treatment selection over the course of the period of highest risk. In their meta-analysis, Van Meter et al. noted that the initial prodrome is sufficiently long for early identification efforts; however, the duration of subthreshold symptoms tends to be short before recurrence. Hence, close *prospective* monitoring for subthreshold or risk syndromes is essential [20], especially since youth offspring of parents with Bipolar Disorder experience pluripotent outcomes. In their study Hafeman et al. found that the strongest predictors of new-onset bipolar spectrum disorders were baseline anxiety/depression, baseline and proximal affective lability, and proximal subsyndromal manic symptoms ($p<0.05$) [21]. They noted that while youth without anxiety/depression, affective lability, and mania (and with a parent with older age at mood disorder onset) had a 2% predicted chance of conversion to a bipolar spectrum disorder, those with the risk factors had a 49% predicted chance of conversion. Given the high frequency of ADHD and anxiety in youth offspring of parents with Bipolar Disorder, some researchers have suggested that these disorders may represent early dimensional predictors or prodromes that precede the development of mania [21,22]. Prodromal Bipolar Disorder symptoms that have been *retrospectively* examined in youth who have already developed mania include syndromal and subsyndromal major depressive disorder, anxiety, episodic subsyndromal manic episodes, ADHD, and disturbances in sleep, energy, and cognition. Subthreshold manic or

hypomanic episodes have been found to be a diagnostic risk factors for the development of manic, mixed, or hypomanic episodes in the offspring of parents with Bipolar Disorder [14]. One large naturalistic prospective study found that 25% of children and adolescents initially diagnosed with subsyndromal Bipolar Disorder symptoms (Bipolar Disorder not otherwise specified), and 20% diagnosed with Bipolar Disorder II, transitioned to Bipolar Disorder I during the 2-year follow up [23]. Thus, both a retrospective understanding of prodromes and a prospective characterization of risk syndromes are critical to guide treatment planning and prevention strategies for Bipolar Disorder [24]. Indeed, interventions used to treat anxiety and ADHD early in the risk period may require a different approach than subthreshold or progressive mania-like symptoms that may present later in the risk period.

Youth at familial risk for Bipolar Disorder have multiple symptom presentations, so the approach to treating them should involve careful consideration of the risks, benefits, and alternative options available through a collaborative discussion with the patient and his/her family. Youth at risk for Bipolar Disorder range from knowing bipolar disorder well through observations of their parent(s) to requiring extensive psychoeducation about associated signs and symptoms. Due to the uncertainty of multifinality in children, discussion of risk and resilience factors can be a source of both anxiety and relief for families with Bipolar Disorder. All families want and need hope for an optimal functional outcome. In this review, we will systematically discuss available treatment options for treatment seeking youth at familial risk for Bipolar Disorder, providing, where available, the level of evidence to support a recommended treatment approach.

METHODS

A literature search using NIH PubMed was conducted to identify peer-reviewed studies of treating children and adolescents with or at risk for bipolar disorder for the period of 1966 to August, 2017. The following terms were included in the search: “medication” or “psychotropic” or “psychotherapy” or “treatment” with “risk,” “bipolar,” and “adolescents,” “children,” “youth,” “juvenile,” or “pediatric,” followed by “depression,” “mania,” “ADHD,” “anxiety,” and “psychiatric symptoms.” References from identified articles were also reviewed to ensure that all relevant papers were included.

RESULTS

Treatment of psychiatric symptoms in high-risk adolescents

In the evaluation and treatment of youth at risk for Bipolar Disorder, there are important nature and nurture factors that contribute to early symptom presentation. Recent research demonstrates that among families affected by Bipolar Disorder, these nature and nurture factors interact and may impact the neurodevelopment of Bipolar Disorder. For example, families with Bipolar Disorder tend to have low cohesion, organization and expressiveness, but high conflict; and chaos in the family may be associated with prefrontal-subcortical disconnectivity [25]. Interventions aimed at improving communication and reducing family stress are beneficial to these high-risk youth [26] and may improve prefrontal regulation of subcortically driven mood dysregulation [27]. In their 16-year prospective cohort study, Duffy and colleagues [28] studied 233 adolescents and their parents who completed clinical

assessments prospectively over a decade [19]. Offspring met DSM-IV criteria for Major Depressive Disorder, dysthymia, cyclothymia, depression not otherwise specified, Bipolar Disorder I, Bipolar Disorder II, Bipolar Disorder not otherwise specified, schizoaffective disorder (bipolar type), substance use disorder, and anxiety disorder. The mean age of onset of mood episodes was 18.3 years (SD: 4.5). Authors found that parent-child relationships, specifically perceived maternal neglect by self-report (regardless of whether mother was the affected parent), was a significant early predictor of mood and anxiety disorders in high-risk offspring, which may increase their emotional sensitivity ($p=0.02$). Research has also shown that those with Bipolar Disorder who had mothers with Bipolar Disorder reported more maternal rejection [29] and had more exposure to maternal negativity [30]. In their prospective study of 189 offspring of a parent with Bipolar Disorder, Goodday et al. found that a longer exposure to parental Bipolar Disorder was associated with a higher risk of mental illness in the offspring [31]. Compared to those who were not exposed to parent Bipolar Disorder during this time, those exposed during the first 2 years of life were found to have significant association with the risk of mood disorder (hazard ratio (HR): 1.1, 95% CI: 1.0–1.2) and there was a 1.5-fold risk of any psychopathology (95% confidence interval (CI): 1.0–2.3) and a 2.5-fold increased risk of substance use disorders (95% CI: 1.2–5.3). These mood and other psychiatric symptoms may represent relevant risk syndromes that could lead to Bipolar Disorder and significant morbidity and mortality. Early intervention may not only alter symptom trajectories, but may also result in more favorable neuroplasticity effects, especially during critical years of development. Treatment of this high-risk group consists of comprehensive early interventions with the primary goal to reduce the burden of risk syndromes and to either prevent or delay progression toward the development of Bipolar Disorder [32]. We will now review sequentially prevention strategies, followed by behavioral, cognitive, psychosocial and psychopharmacological interventions that individually, or in combination, target early symptoms among high-risk youth.

Promoting Resilience to Optimize Outcome: Non-Pharmacological Interventions

It is important to obtain a detailed history of patient’s symptoms, triggers, family history and promote healthy lifestyle habits including regular exercise, adequate sleep, and proper nutrition [33]. Sedentary lifestyle is a common problem among individuals with Bipolar Disorder [34] and may consequently affect youth offspring living with a Bipolar Disorder parent. The beneficial effects of exercise on depressive symptoms in broad samples of treatment seeking youth have been meta-analytically reviewed [35], but have not been specifically demonstrated in youth at risk for Bipolar Disorder.

Offspring of parents with Bipolar Disorder also have a number of sleep disturbance symptoms, including excessive daytime sleepiness, headaches after awakening, and nightmares compared to youth offspring of parents without Bipolar Disorder [36]; poor sleeping high-risk youth are more likely to develop Bipolar Disorder compared to good or variable sleepers [37], with a potentially negative impact of shortened sleep duration on ventral striatum-insula brain connectivity during reward processing [38]. These studies suggest that sleep is an important early target for intervention in high-risk youth, but no studies to date have evaluated a sleep intervention in youth offspring of parents with Bipolar

Disorder. Several randomized controlled trials (RCT) have been conducted in broader high-risk youth populations. For example, youth with high levels of anxiety and sleeping difficulties were randomized to either a sleep improvement intervention or an active control study skills intervention [39]. The sleep intervention in this RCT, which included cognitive-behavioral and mindfulness-based therapies, was found to reduce sleep initiation problems and related daytime dysfunction, along with concomitant anxiety symptoms in these youth. Another RCT in children (5–12 years) with ADHD who were randomized into two different groups (sleep hygiene practices and standardized behavioral strategies vs usual clinical care which routinely did not involve assessment and management of sleep problems) found that the active treatment group noted benefit in both sleep and behavioral issues, including ADHD symptoms [40]. Another sleep intervention study targeting infant offspring of parents with depression, found improvement in parental depression, limit setting, sleep quality, and fatigue [41]. Together, these studies provide a reasonable level of evidence that youth offspring of parents with Bipolar Disorder could benefit from sleep-related interventions.

Nutritional interventions may be particularly appealing in youth offspring of parents with Bipolar Disorder due to its favorable side effect profile. In recent years, omega-3 fatty acids have been evaluated for their efficacy in youth with or at risk for Bipolar Disorder, with some success when compared to placebo, especially when combined with psychoeducational psychotherapy. Omega-3 fatty acids have neurotrophic and neuroprotective properties. In a pilot randomized controlled trial, 23 children and adolescents (ages 7–14 years) with a diagnosis of Bipolar Disorder not otherwise specified or cyclothymia were randomized to 12 weeks of omega-3 versus placebo and individual family psychoeducational psychotherapy versus active monitoring [42]. Intent-to-treat analyses indicated significant improvement in depressive symptoms for combined treatment relative to placebo, active monitoring ($p = 0.01$, $d = 1.7$) as well as omega-3 therapy. Side effects were uncommon and mild. Wozniak et al. also conducted a 12-week, double blind RCT to evaluate the effectiveness and tolerability of high eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) omega-3 fatty acids and inositol as monotherapy and in combination in children (5–12 years) who met DSM-IV diagnostic criteria for Bipolar Disorder I or II or Bipolar Disorder not otherwise specified and displayed mixed, manic, or hypomanic symptoms. Participants randomized to the omega-3 fatty acids plus inositol arm had the largest score decrease comparing improvement from baseline to end point on the YMRS ($P < .05$), Children's Depression Rating Scale ($P < .05$) and the Brief Psychiatric Rating Scale ($P < .05$). The study did not include severely ill participants, the sample size was small (N=24) and only 54% subjects (N=13) completed the study [43].

Psychotherapeutic Interventions (Table 1)—Family-focused treatment (FFT), psychoeducational psychotherapy, and child and family-focused cognitive-behavioral therapy have been known to be particularly efficacious in youth offspring of parents with Bipolar Disorder. These treatments are family based, focus on providing psychoeducation on symptoms and symptom management to the families and training of families in communication, problem solving as well as emotion regulation. However, most of these trials are limited by the small sample size.

Miklowitz et al. studied a sample of 13 offspring of parents with bipolar disorder, (mean 13.4±2.79 years) who met DSM IV criteria for Major Depressive Disorder (n=8), cyclothymic disorder (n=1), or Bipolar Disorder not otherwise specified (n=4). These families received 12 sessions of FFT adapted for youth at high risk for Bipolar Disorder (FFT-HR) over 4 months, along with psychotropic medications. These children were followed for a year and showed significant improvements in depression, hypomania, and psychosocial functioning scores on the Adolescent Longitudinal Interval Follow-up Evaluation, as well as significant improvements in Young Mania Rating Scale (YMRS) and [F (1,33) = 13.0, p < 0.001; d = 1.15, SE = 0.4] Children's Depression Rating Scale scores [F (1,40) = 6.7, p = 0.013; d = 0.63, SE = 0.40] [44]. This study was followed by the same group with an RCT to compare FFT-HR (12 week session over 4 month of psychoeducation and training in communication and problem-solving skills) with an educational control treatment (1–2 family sessions). In this study, researchers found that youth in the FFT group had more rapid recovery from initial mood symptoms (hazard ratio = 2.7, $p = .047$), more weeks in remission [mean = 27 weeks, 95% CI = 24.–30) when compared to youth in the control group (mean = 20 weeks, 95% CI = 17– 22) (χ^2 [1] = 15.8, $p < .0001$], and a more favorable trajectory of YMRS scores over 1 year than youth in the educational control group [26].

Goldstein et al. conducted an open trial of Interpersonal and Social Rhythm Therapy (IPSRT), which consisted of 12 sessions over 6 months in 13 adolescents. IPSRT is known to delay Bipolar Disorder recurrence in adults by stabilizing their daily routines and sleep-wake cycles [45]. All youth had a first degree relative with Bipolar Disorder, although 50% were healthy at baseline and the other 50% had subthreshold internalizing/externalizing disorders. Data suggested a significant change in select sleep/circadian patterns (i.e., less weekend sleeping in and oversleeping), however participants attended only half of the scheduled sessions due to parental Bipolar Disorder illness severity. Authors concurred that IPSRT focus on stabilizing daily rhythms and interpersonal relationships may be beneficial for these youth, however, there is a need controlled trials with longitudinal follow-up to assess whether this intervention can help prevent or delay onset of disorder in these youth.

To assess effectiveness of non-pharmacologic treatments for anxiety in youth offspring of parents with Bipolar Disorder, Cotton et al. conducted an open pilot trial of a 12 weekly mindfulness-based cognitive therapy for children (MBCT-C) [47]. MBCT-C is a manualized group psychotherapeutic intervention that incorporates cognitive behavioral principles and mindfulness exercises to enhance attention regulation and non-judgmental acceptance of thoughts expressions and emotions in the moment. Authors found that following intervention, the 10 adolescents (mean age = 13.2 years) that participated (diagnosed with generalized, social and/or separation anxiety disorders), clinician-rated anxiety as well as youth-rated trait anxiety were significantly reduced (mean before = 11.1; mean after = 4.3; P < 0.01) and (P = 0.03) respectively. Families also reported high levels of feasibility, acceptance and usefulness of MBCT-C. Increased mindfulness was associated with decreased anxiety. MBCT was also associated with increased activation in the bilateral insula, lentiform nucleus, thalamus, left anterior cingulate while viewing emotional stimuli during a continuous performance task [48]. Importantly, reduction in anxiety was correlated with change in activation in the bilateral anterior insula and anterior cingulate during the

viewing of emotional stimuli. Thus, a mindfulness based treatment approach in youth at risk for Bipolar Disorder can reduce anxiety symptoms and have corresponding improvement in neural function.

In a recent pilot randomized trial (n=42) of Interpersonal and Social Rhythm Therapy plus Data-Informed Referral (IPSRT+DIR) versus DIR-alone for adolescents, aged 12–17 years, at-risk for Bipolar Disorder, authors found that IPSRT may help delay or prevent subthreshold hypo/manic symptoms among at-risk youth by enhancing sleep continuity [46]. These data are not yet published.

Psychopharmacological management (Table 2)

A few limited studies have evaluated the efficacy of pharmacological interventions for the treatment of symptoms in youth at risk for Bipolar Disorder, and the literature is currently mixed. Indeed, youth at risk for Bipolar Disorder have variable exposures to medications, sometimes going years before receiving adequate treatment, and on other occasions, receiving multiple trials of medications before stabilizing. Chang et al. studied 106 children and adolescents who had at least one parent with Bipolar Disorder to investigate the relation between exposure to psychotropic medications prior to first manic episode and age at onset, which was determined as nearest month of first manic or hypomanic episode [53]. Sixty-three of the 106 subjects studied met criteria for Bipolar Disorder I or II, and the other 43 had subsyndromal mood symptoms that did not meet criteria for Bipolar Disorder. This study found that children who had Bipolar Disorder or subsyndromal symptoms were exposed to multiple psychotropic medications, even before the onset of a full manic episode. Exposure to stimulants or antidepressants was not predictive of an earlier age at onset of Bipolar Disorder. However, exposure to mood stabilizers prior to the first manic episode was associated with a later age at onset of mania. Like most psychotherapy trials described above, several pharmacological trials in high-risk offspring are limited due to small sample size and show mixed results. Specifically, although open label trials have yielded some efficacy of mood stabilizers or antipsychotics, these results have not been replicated in RCTs. We will now summarize these studies by their level of evidence.

Double blind placebo controlled trials—A 6-week, double-blind, placebo-controlled RCT performed in 30 pre-pubertal depressed children with family history predictors of future bipolarity (Bipolar Disorder I or mania in first or second degree relatives or a multigenerational/loaded Major Depressive Disorder family history) aimed to evaluate the efficacy of lithium (17 randomized to lithium group and 13 to placebo; mean age 10.7 ± 1.2 years). Results found that lithium was no more efficacious than placebo and four participants discontinued due to side effects [49].

Findling et al. conducted a double blind RCT in 5–17 year old offspring of a parent with Bipolar Disorder, who met DSM IV criteria for Bipolar Disorder not otherwise specified or cyclothymia. Symptomatic high-risk youth in this double-blind, placebo-controlled trial were either randomized to divalproex monotherapy or a placebo [51]. Results showed that while both groups [divalproex sodium (N = 29) or placebo (N = 27)] improved in

psychosocial functioning and mood symptoms over time (p values < .002), they did not significantly differ in clinically meaningful outcomes (most significant p > .14).

In another study, Findling et al. studied nine 7–16 year old high risk offspring of parents with Bipolar Disorder, who were randomized to receive treatment with either paroxetine or a combination of paroxetine-divalproex sodium [54]. Neither treatment in this study was particularly effective in the management of depressive symptoms, and over half of the patients suffered from a manic episode, hypomanic symptoms, or suicidality during treatment. This study raised concern that risk may outweigh benefit in treating symptoms in youth at risk for Bipolar Disorder.

Finally, Findling et al. conducted a double-blind placebo-controlled trial recently published to compare the superiority of aripiprazole to placebo in children and adolescents (N=59, 5–17 year old) at familial risk for bipolar disorder, based on having a parent with bipolar I disorder, and at least one additional first-or-second-degree relative with a mood disorder. Youth in this trial met DSM-IV criteria for BD-NOS or cyclothymia. At 12 weeks, aripiprazole was superior than placebo in reducing symptoms of mania in this population ($p<0.005$, effect size: Cohen's $d=1.16$). However, there was a significant difference in weight gain in the two groups (aripiprazole: 2.3 kg [SD = 3.3]; placebo: 0.7 kg [SD = 1.8]) [55].

Open-label trials—In contrast to the relatively negative results presented in the RCTs above, several open-label studies in youth at risk for Bipolar Disorder have demonstrated efficacy for the treatment of risk syndrome related symptoms. In a prospective open trial, Chang et al. enrolled 24 high risk offspring, who had DSM IV diagnoses of Major Depressive Disorder, dysthymic disorder, cyclothymia or ADHD [50], and at least moderate levels of mood symptom severity. These children were treated with divalproex sodium for 12 weeks with a mean final dose = 821 mg/ day and a mean final serum level = 79 mcg/ ml. Authors found that out of 23 participants (one discontinued due to ongoing symptoms), 18 (78%) were considered responders on the Clinical Global Impressions-Improvement (CGI-I) scale. While studying the neural effects of divalproex in high-risk youth, Chang et al. found that the degree of decrease in prefrontal brain activation correlated with degree of decrease in depression severity [56]. Although divalproex was well tolerated, this study was limited by a heterogeneous sample, lack of placebo group, small sample size, and a limited 12-week treatment period.

In another open-label single-blind 12 week prospective open study, DelBello et al. investigated the effectiveness of quetiapine in youth offspring of parents with Bipolar Disorder, where youth met criteria for a variety of non-Bipolar Disorder-I psychiatric disorders, including Bipolar Disorder not otherwise specified (N=11), dysthymia (N=3), Bipolar Disorder II disorder (N=3), cyclothymia (N=2), and Major Depressive Disorder (N=1) [52]. Adolescents were considered symptomatic if they scored ≥12 on YMRS or ≥ 28 on Childhood Depression Rating Scale-Revised Version (CDRS-R). At week 12, 87% of the patients were considered responders. While adverse effects such as weight gain and sedation were reported, no adolescents discontinued medication due to them. It could be argued that the small sample of youth in this study were already on the bipolar spectrum and may no longer be considered “high-risk” or comparable to at-risk youth in other studies.

Risk of antidepressant induced mania-like symptoms (AIMS)—Several case reports have described mania, hypomania, or mania-like symptoms in pediatric patients with or at risk for Bipolar Disorder while concurrently being treated with selective serotonin reuptake inhibitors (SSRIs) [57], and occurring between 2 weeks to up to one year following SSRI exposure. In their study of youth with mood symptoms and at least one parent with Bipolar Disorder, Baumer et al. found that 36% (8/22) experienced AIMS, defined as at least 1 day of mania [58]. This rate was much higher than other RCTs of youth with depression or anxiety, exposed to SSRI, but had no genetic loading for Bipolar Disorder (<20%). As above, in a small prospective study that investigated SSRI treatment (paroxetine) in youth at risk for Bipolar Disorder, fifty percent of youth developed manic symptoms, regardless of adjunctive divalproex treatment [54]. In another recent prospective evaluation of 118 9–20 year old youth offspring of parents with Bipolar Disorder followed over nearly five years, 21% of youth had antidepressant exposure, of which 57% experienced an adverse event (e.g. irritability, aggression, impulsivity, or hyperactivity) that led to discontinuation of the antidepressant [59]. Those patients who experienced an adverse reaction were significantly younger than those who did not ($p = 0.02$) and discontinuation of antidepressant therapy secondary to an adverse event occurred at an average of 17 ± 17 weeks (median: 11 weeks, range: 2–57 weeks). Collectively, these studies suggest that antidepressant medications may be poorly tolerated in youth at familial risk for Bipolar Disorder [60]. This issue merits further systematic and critical evaluation using larger sample sizes and in an RCT design.

Despite limitations of prior reports, clinicians generally proceed with caution while treating depressive symptoms in youth at risk for Bipolar Disorder. Risk for antidepressant-induced mania, which seems to increase among youth with a bipolar family history [60], underscores the importance of obtaining a careful family psychiatric history and evaluating for the presence of mania-like symptoms in all youth being prescribed an antidepressant. Youth at risk for Bipolar Disorder presenting initially with psychiatric symptoms commonly receive a trial of psychotherapy prior to starting a pharmacological agent. Moreover, due to the limited evidence for efficacy of pharmacological treatment in this high-risk population, evidence-based psychotherapeutic techniques, as mentioned above, remain a cornerstone initial treatment. If therapy is ineffective or depressive symptoms are moderate to severe with sufficient functional impairment, existing nonpharmacological and pharmacological treatments that have demonstrated proven efficacy in broader pediatric populations may be cited and used to guide treatment decisions. To date, there are no RCTs demonstrating the efficacy and safety of antidepressants for the treatment of depression or anxiety symptoms in youth offspring of parents with Bipolar Disorder, but antidepressants are the standard of care after or in combination with psychotherapy for the treatment of these symptoms in youth with depression or anxiety, regardless of family history. Cautious selection of an antidepressant with slow titration and careful monitoring may be one of those initial options. SSRIs are still considered first line treatment of depression in children and adolescents. Currently, fluoxetine and escitalopram are the only Food and Drug Administration (FDA)-approved agents for the treatment of depression in youth. While fluoxetine has the most evidence for efficacy in this population, there are concerns about its use in youth at risk for antidepressant-induced mania given its long half-life. All antidepressants, though, carry a risk of activation or switch to hypomania/ mania, especially in high-risk youth. If a youth

experiences a subsequent treatment-emergent mania or mania-like activation symptoms that are clinically meaningful to warrant discontinuation of the antidepressant, possible next options in the management of mood symptoms might include use of mood stabilizers such as lamotrigine or lithium or an atypical antipsychotic. While there is less risk of activation with these agents, there are limited data regarding the use of lithium and lamotrigine for treatment of depression in adolescents (e.g. one negative RCT with lithium) [61]. Importantly, the olanzapine-fluoxetine combination has received FDA approval for the treatment of depression in Bipolar Disorder due to positive efficacy data [62]. However, its number needed to harm (NNH = 3) for weight gain detrimentally prevails over its number needed to treat (NNT = 6). In addition, atypical antipsychotics may have a role in the treatment of mood disorders in those who experience or are at risk for antidepressant-related activation symptoms. However, risks and benefits of this class of medications should be carefully weighed given the potential for development of metabolic syndrome. Lurasidone has been found to have better tolerability in this population in doses <120 mg/day. However, all of these agents require further study to establish an evidence base for safety and efficacy for the treatment of depression, anxiety, or other risk syndromes in youth at risk for Bipolar Disorder [63].

Stimulants and Bipolar Disorder onset—To date, no RCTs have examined efficacy and safety of ADHD treatment in youth at risk for mood disorders. Nevertheless, extensive evidence suggests that stimulant medications can improve the core symptoms of ADHD including inattention, distractibility, impulsivity and hyperactivity. Research has yet to demonstrate that medications or other interventions change the underlying course of ADHD. Studies have shown that in children with Bipolar Disorder, severe mood dysregulation or disruptive mood dysregulation, the addition of stimulants, along with mood stabilizers can lead to better treatment response and that conversion from ADHD to Bipolar Disorder or severe mood dysregulation occurs less often in children who receive stimulants than in children who do not receive stimulants [64]. In addition, recent evidence suggests that among youth with mania, the mood symptoms should be addressed first and if residual ADHD symptoms persist and impact functioning, then an additional medication for ADHD should be considered [65,66].

CONCLUSIONS AND FUTURE DIRECTIONS

Despite progress in research on the detection of early risk factors as well as characterization of prodromal clinical features, there is paucity of evidence regarding interventions that could prevent the progression of prodromal symptoms to full-blown Bipolar Disorder or other psychiatric disorders in high-risk offspring of parents with Bipolar Disorder. Since childhood and adolescence are periods of rapid and dynamic changes in cortical maturational processes that are sensitive to perturbations, psychotropic medications may alter typical brain development trajectories toward more favorable outcomes [67,68]. Although it is important to intervene early and prevent a first episode, not all youth at risk develop Bipolar Disorder. It is still vital to study this group as it may help identify protective factors that prevent the development of Bipolar Disorder in this youth. They may still be at high risk of developing recurrent depression. Hence, treatment with no or minimal risks

should be offered first line, carefully weighing the risks versus benefits of psychotherapeutic and pharmacological treatments. In children and adolescents who are at high risk of developing a Bipolar Disorder, initial approach should aim at lifestyle changes, including regular physical activity or exercise and good sleep hygiene, proper nutrition, followed by social rhythm, family-based, and individual or group psychotherapeutic interventions. In order to prevent a switch to a hypomanic or manic episode, patients should be monitored carefully if an antidepressant is started for depression or anxiety symptoms, starting at a low dose and titrating with careful attention to any treatment-emergent adverse events. If antidepressants do not work or result in adverse events, mood stabilizers or newly emerging atypical antipsychotic medications that have favorable risk/benefit profiles may be reasonable alternatives.

Thus, a family history is among the clearest risk factors for developing Bipolar Disorder. Early changes in brain function may precede mood symptoms and interventions may prevent or potentiate the natural course of mood problems before reaching adulthood. Our field needs more maintenance and long-term outcome studies as well as combination (pharmacotherapy and psychotherapy) trials to provide an evidence-based approach to treating symptomatic high-risk youth. Studies of prodromes can also help identify biomarkers of Bipolar Disorder relapse [69], which then could be target interventions to prevent chronicity of the illness. There is currently insufficient evidence for treating high-risk youth with treatment emergent mania. We need more prospective studies to identify those at highest risk for developing mania and its management when it occurs in the context of treating depression, anxiety, or ADHD symptoms. Ongoing research should be aimed to evaluate reliable biomarkers that identify youth at highest risk for functional impairment due to psychiatric symptom burden, and provide individualized treatment approaches that best fit the needs of the child and the system in which they live.

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Table 1

Psychotherapy Studies in High-Risk Bipolar Offspring

Authors	Sample Population and Size	Intervention	Design	Outcome
Miklowitz, et al. 2011.	13 children with a parent with Bipolar I or II Disorder and with active mood symptoms	Family Focused Therapy for Youth at High-Risk for Bipolar Disorder (FFT-HR)	Open, pilot 12 sessions over 4 months	Improved depression, hypomania, and psychosocial functioning scores.
Miklowitz, et al. 2013.	40 youth with BD-NOS, MDD or cyclothymia with a first degree relative with Bipolar I or II disorder and active mood symptoms	12 sessions of FFT-HR or 1–2 sessions of education control (EC)	RCT of FFT-HR versus EC	More rapid recovery from initial mood symptoms, more weeks in remission, and a more favorable trajectory of Young Mania Rating Scale (YMRS) scores over 1 year than youth in EC.
Goldstein, et al. 2014.	13 adolescents with a first degree relative with BD; 50% healthy at baseline, 50% with internalizing/externalizing disorders	Interpersonal and social rhythm therapy (IPSRT)	Open, pilot 12 sessions over 6 months	High satisfaction but only attended about half of scheduled sessions due to parental BD illness severity; less weekend sleeping in and oversleeping with treatment.
Cotton, et al. 2015.	10 high-risk offspring with at least 1 bipolar parent and with anxiety symptoms	Mindfulness based cognitive therapy for children (MBCT-C)	Open, pilot 12 week	Reduced clinician-rated anxiety and youth-rated trait anxiety; Increased parent-rated emotion regulation; Increased mindfulness associated with decreased anxiety.
Goldstein 2017.	42 adolescents, aged 12–17 years, at high risk for BD	Interpersonal and Social Rhythm Therapy plus Data-Informed Referral (IPSRT+DIR) versus DIR-alone	Pilot, randomized, 8 sessions	IPSRT may help delay or prevent subthreshold hypo/manic symptoms among at-risk youth by enhancing sleep continuity

Table 2

Pharmacological Studies in High-Risk Bipolar Offspring

Authors	Sample Population and Size	Drug	Design	Outcome
Geller, et al. 1998.	30 Prepubertal (mean age 10.7 years) depressed children; 80% had Family History of BP-I or mania (40% of parents had BP-I or mania); and 20% with loaded or multigenerational MDD but no mania	**Lithium** (n=17) versus placebo (n=13)	6-week Double-blind placebo controlled	**No difference** between active and placebo groups
Chang, et al. 2003.	24 (6–18 year old) youth with mood and behavioral disorders and at least one parent with BD	**Divalproex**	12-week open-label trial	**78% response rate**; no discontinuations due to adverse effects
Findling, et al. 2007.	56 symptomatic youth (ages 5–17) with BD-NOS or cyclothymia with at least one parent with BD	**Divalproex (n=29) versus placebo (n=27)**	Double-blind placebo controlled trial with upto 5 year follow up	**No difference** in survival time for discontinuation for any reason (p=.93) or due to a mood event (p=.55)
DelBello, et al. 2007.	20 symptomatic adolescents (12–18 years old) with at least one first-degree relative with BD I	**Quetiapine**	12-week single blind open-label trial	**87% response** (CGI-I < or=2) at week 12; decreased YMRS and children's depression rating scale (CDRS) scores from baseline to endpoint
Findling, et al. 2009.	9 children (7–16 years old) with MDD and at least one parent with BD	**Paroxetine (n=4) versus Paroxetine +Divalproex (n=5)**	1:! Randomization to open-label treatment	**Neither treatment was effective;** 50% had mania symptoms
Findling et al. 2017	(5–17 years old) with cyclothymia or BD-NOS and at least one parent with BD and a second degree relative with a mood disorder and not responsive to psychotherapy	**Aripiprazole (n=30) vs placebo (n=29)**	12-week double blind placebo controlled trial	Aripiprazole was superior to placebo in reducing symptoms of mania; youth who received aripiprazole vs placebo had significantly more weight gain (mean 2.3 vs 0.7 kg)