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Interventions for Youth at High Risk for Bipolar Disorder and Schizophrenia

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Synopsis

Increasing evidence from retrospective and prospective studies is beginning to validate criteria to identify individuals at high risk for developing bipolar disorder or schizophrenia. In parallel, intervention trials are evaluating the efficacy and tolerability of pharmacological and non-pharmacological approaches for the treatment of sub-threshold and possibly prodromal presentations in these high-risk populations with the ultimate objective of mitigating illness progression. This article reviews current evidence for candidate interventions for high-risk individuals in an effort to guide future research in this rapidly emerging field.

Keywords

BIPOLAR DISORDER; MANIA; SCHIZOPHRENIA; PSYCHOSIS; PEDIATRIC; ADOLESCENT; PREVENTION; CLINICAL STAGING; ATYPICAL ANTIPSYCHOTICS; ANTIDEPRESSANTS; OMEGA-3 FATTY ACIDS

OVERVIEW

Bipolar disorder (BP) and schizophrenia (SZ) are chronic and typically recurring illnesses with significant psychosocial morbidity and excess premature mortality. Increasing evidence from retrospective and prospective studies is beginning to elucidate prodromal criteria to identify individuals that are at 'high risk' (also termed 'ultra-high risk') for developing mania, and by definition BP-I or SZ. In general, high risk criteria involve having a first-degree relative with BP or SZ, a history of sub-threshold mood or psychotic symptoms, and being in the age range most frequently associated with the initial onset of BP or SZ (i.e., adolescence). While ongoing research is seeking to validate and refine these criteria, there is also increasing experimental interest in developing and evaluating interventions that can be delivered prior to the initial onset of manic or psychotic symptoms to slow or prevent illness progression in high risk populations. Additionally, potential negative effects associated with conventional pharmacological interventions used to treat co-morbid symptoms in the

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prodromal stage indicate a need for alternative treatment approaches. In this article, we summarize evidence for potential interventions for high risk individuals and highlight associated ethical and safety considerations.

Bipolar disorder is typically characterized by recurrent episodes of mania and depression, as well as inter-episode periods of euthymia. In the United States (U.S.), lifetime prevalence estimates of BP are 1.0% for BP-I, 1.1% for BP-II, and 2.4% for subthreshold BP (4.4% total) [1]. The initial onset of BP typically occurs during adolescence [2], with a lifetime prevalence of adolescents having BP-I or II in the US of 2.5% [3]. Family and twin studies indicate that the etiology of BP involves both genetic and environmental factors, and having a first-degree relative with BP or unipolar depression substantially increases the risk for developing BP compared with the general population [4]. Untreated patients with BP typically exhibit progressive increases in the frequency and severity of manic and depressive episodes over time, and mood-stabilizers and second generation antipsychotics (SGAs) are widely prescribed for the treatment and prevention of mood episodes in patients with BP.

Mood symptoms commonly exhibited by children and adolescents prior to the initial onset of mania include syndromal and subsyndromal major depressive disorder (MDD), anxiety, and episodic subsyndromal manic symptoms (sleep disturbances, anger/irritability, increased energy, and rapid mood fluctuations termed ‘cyclotaxia’) [5–8]. For example, Strober and Carlson [9] found that 20% of adolescents with MDD developed BP-I over 3 to 4 years, especially if they had a family history of BP, rapid symptom onset, or psychosis. Furthermore, a prospective study found that 38% of children and adolescents initially diagnosed with subsyndromal BP symptoms (BP-not otherwise specified), and 25% diagnosed with BP-II, transitioned to BP-I during the 4-year follow-up [10]. Cognitive symptoms, particularly deficits in concentration/attention, also frequently precede the initial onset of mania. Indeed, the high rate of comorbid attention deficit hyperactivity disorder (ADHD) in pediatric BP, as high as 98%, and lower age at onset of mania in patients with comorbid ADHD, are consistent with ADHD being a prodromal feature in a subset of patients [11]. One research group has proposed criteria for individuals at high risk for developing BP-I (termed bipolar at-risk, BAR), which included having a first degree relative with BP-I, a history of sub-threshold mania, MDD, and/or rapid mood fluctuations (cyclothymia), and being younger than age 25 years [12]. Using these criteria, they found that 23% of help-seeking patients meeting these high risk criteria transitioned to threshold mania within an average follow-up period of 265 days compared with 0.7 percent of patients not meeting BAR criteria [12]. Other groups have proposed high risk criteria based on the presentation of prodromal clinical features, ADHD, and other putative risk factors and endophenotypes [8,13].

Schizophrenia (SZ) is a progressive psychiatric disorder with a life-time prevalence rate of approximately 1%, and is typically characterized by positive (delusions, hallucinations, incoherent speech) and negative (apathy, depression) symptoms and cognitive impairments (memory, attention).Concordance rates among monozygotic twins indicates both genetic and non-genetic factors play a pathogenic role, and males are at greater risk of developing SZ [14]. The initial onset of psychosis typically occurs in late adolescence or early adulthood, and first-episode psychotic patients are typically prescribed SGA medications. The initial onset of psychosis is frequently preceded by a prodromal period of approximately 1 to 5 years which is associated with sub-threshold psychotic symptoms, negative symptoms, MDD, cognitive impairments, and impaired social and occupational functioning [15]. While there is currently no consensus regarding high risk criteria, ‘ultra high risk’ criteria have been more extensively evaluated and require attenuated psychotic symptoms (defined using PANNS scores), transient psychosis, and/or schizotypal personality disorder or a first-degree relative with DSM-IV psychotic disorder [16]. A recent meta-analysis of 27 prospective

studies of 2,502 'high risk' patients found a consistent and increasing risk of psychosis transition over 3 years [17]. It is also important to note that transition to psychosis does not equate with transition to SZ, and a recent meta-analysis of 23 prospective studies of 2,182 high risk patients found that only a small percentage of high risk patients (15.7%) who transition to psychosis subsequently receive a formal diagnosis of SZ [18].

EMPIRICAL EVIDENCE FOR ETHICAL ISSUES

While establishing effective and safe early intervention strategies is of critical importance for minimizing the significant morbidity and mortality associated with the progression of mood and psychotic disorders, there are several ethical dilemmas that the field needs to consider.

- First, the consequences of labeling children and adolescents with a "prodromal" diagnosis will be need to be deliberated, as illustrated by the controversy surrounding whether a diagnosis of 'Risk Syndrome of Psychosis', which consists of subthreshold or attenuated positive psychotic symptoms that are sufficiently distressing and/or disabling to the patient, should be added to *DSM-V* [19].
- Second, because the initial onset of mania and psychosis most frequently occurs during adolescence, a developmental period associated with rapid and dynamic changes in both regressive (i.e., synaptic pruning) and progressive (i.e., myelination) cortical maturational processes [20], understanding the long-term impact of pharmacological medications on brain developmental trajectories represents an important consideration, particularly in view of preclinical evidence that psychotropic medications significantly alter normal brain development [21–23].
- Third, early intervention studies need to better assess the short- and long-term impact of 'standard of care' treatment strategies for prodromal symptomatology (e.g. depression, inattention and hyperactivity). As discussed below, antidepressant and psychostimulant medications used for these early manifestations of incipient mania may hasten illness progression in high risk youth.
- Lastly, SGA medications, which may be efficacious for the treatment of mood and sub-threshold psychotic symptoms in high risk youth, are frequently associated with significant treatment-emergent weight gain and obesity, metabolic syndrome, and elevated cardiovascular risk factors in adolescent patients [24].

Together, these data highlight potential risks associated with the use of pharmacological medications for the treatment of prodromal symptoms in high risk individuals, and endorse the adoption of a 'clinical staging model' [8,25]. The clinical staging model proposes that interventions with lower risks (including psychosocial therapy) may be appropriate for the treatment of sub-threshold symptoms in earlier stages of the illness, whereas those with greater risks reserved for threshold symptoms emerging at later stages [25].

TREATMENT OF BIPOLAR DISORDER IN THE PRESENCE OF CO-MORBID CONDITIONS

As discussed, MDD frequently precedes the initial onset of mania and is commonly treated with antidepressant medications regardless of the risk for developing BP. However, an emerging body of evidence suggests that treatment with antidepressants may precipitate or exacerbate suicidality and manic symptoms and possibly reduce the age at onset of mania [26].

An epidemiological study found that peripubertal children (age 10 to 14 years) exposed to antidepressants were at highest risk for manic conversion [27], and another study found that children who received prior antidepressant treatment had an earlier onset of BP than never exposed children [28]. A retrospective study found that 5 of 6 (83%) adolescent/young adult patients transitioning to mania were previously treated with a selective serotonin reuptake inhibitor (SSRI) antidepressant [12]. Additionally, in a cohort of 52 children and adolescents with or at high risk for BP, 50% had experienced antidepressant-induced mania, and 26% experienced new onset suicidal ideation within one month of starting an antidepressant [29]. In a small (n=9) prospective open-label treatment trial, over 50% of youth at high risk for BP experienced new manic symptoms or suicidality following treatment with paroxetine or paroxetine plus divalproex [30].

Together, these data highlight the potential vulnerability of youth at high risk for BP to serious psychiatric side effects of antidepressant medications. Of additional concern is that these medications may cause “kindling” towards an earlier onset of mania than otherwise would have occurred [31]. It is possible that such side effects as mania or suicidality may create a type of neurobiological “scar” that accelerates the development of mania in response to psychosocial stress [32], though retrospective data have not supported this acceleration model of mania onset [33]. Furthermore, MDD is also a common feature of the psychosis prodrome [34], and preliminary evidence suggests that antidepressants may be *protective* against the development of psychosis in high-risk patients [35,36]. Therefore, additional prospective research is needed to evaluate the risks and benefits associated with antidepressant treatment in youth at risk for BP and SZ.

Cognitive symptoms, particularly deficits in concentration/attention, also frequently precede the initial onset BP and SZ, and are commonly initially treated with psychostimulant medications, including methylphenidate or amphetamine (AMPH) derivatives. While the role of early treatment with psychostimulants in the pathoetiology of mania or psychosis is poorly understood, acute treatment with psychostimulants may produce clinical features that are analogous to idiopathic mania, and repeated AMPH treatment is associated with psychotogenic effects in a subset of individuals [37]. Moreover, the incremental increase in psychomotor responses (i.e., increased eye-blink rate, arousal, euphoria) observed in healthy controls following repeated AMPH treatment is not exhibited by first-episode manic or psychotic patients [38], and may reflect presensitization in response to prior exposure to psychostimulants or stress [39]. Adolescents with BP and a history of stimulant exposure prior to the onset of BP may have an earlier age at onset of mania than those without prior stimulant exposure, independent of co-occurring ADHD [40]. Thus, psychostimulants may share similar problematic psychiatric effects with antidepressants in youth at high-risk for BD and SZ [26]. Although controlled trials have found that treatment with psychostimulants are effective and largely safe for treating ADHD symptoms in BP youth in conjunction with mood-stabilizers [41–43], it is not clear that such treatment is either safe or effective in youth at high risk for developing BP who have not yet developed mania. In view of evidence for a 7-fold increase in AMPH prescriptions for children in the US over the last decade [44] in parallel with a 40-fold increase in the diagnosis of childhood and adolescent BP in office-based medical settings [45], there is an urgent need for additional research into potential iatrogenic effects of early psychostimulant treatment in high risk populations.

EVIDENCE-BASED INTERVENTIONS

High risk for psychosis

In conjunction with the development of criteria for identifying individuals at high risk for psychosis, preliminary efforts have been made to develop interventions that are protective against the progression to psychosis in high risk patients (Table 1). The first controlled

prevention trial randomized a cohort of patients meeting high risk criteria for psychosis to low-dose risperidone (mean dose, 1.3 mg/d, n=31) combined with cognitive behavioral therapy (CBT) or to need-based supportive psychotherapy (n=28) for 6 months, after which patients were offered ongoing needs-based intervention for an additional 6 months [46]. By the end of the 6-month treatment phase, 10 of 28 (36%) patients who received needs-based supportive psychotherapy transitioned to psychosis compared with 3 of 31 (10%) patients receiving risperidone+CBT (p=0.03). During the 6-month follow-up phase, another 3 patients in the risperidone+CBT group became psychotic and the original treatment group difference became non-significant. However, protection against transition was observed for patients that were adherent to risperidone therapy during the initial treatment phase. In a subsequent larger (n=115) replication study, no differences were found in psychosis transition rates between high risk participants who received 6 months of risperidone +cognitive therapy compared with those who received placebo+cognitive therapy [47]. In the latter study, a greater percentage of patients in the risperidone arm experienced weight gain (30%) compared with placebo (9.1%), though this difference was not statistically significant.

High risk for schizophrenia

Another trial randomized patients at high-risk for SZ to olanzapine (5 to 15 mg/day, n=31) or placebo (n=29) for a 1-year double-blind treatment period followed by a 1-year no-treatment observational period [48]. During the treatment phase, 5 of 31 (16.1%) patients receiving olanzapine and 11 of 29 (37.9%) patients receiving placebo transitioned to psychosis, although this difference did not reach statistical significance (p=0.08). The hazard ratio of conversion to psychosis for placebo-treated patients was 2.5 times greater than olanzapine-treated patients (p=0.09). Prodromal positive symptoms improved more in the olanzapine group than in the placebo group between weeks 8 and 28 (p=0.03). Olanzapine-treated patients gained significantly more weight than placebo-treated patients, and the rate of discontinuation was higher in the olanzapine (55%) than placebo (34%) arm. In the 1-year follow-up period, psychosis transition rates did not differ significantly between treatment groups.

A prospective naturalistic treatment study compared 48 adolescents at high risk for developing SZ treated with antidepressant (n=20) or SGA (n=28) medications [35]. Of the 12 of 48 (25%) patients who transitioned to psychosis, all were prescribed SGAs whereas none of the antidepressant-treated adolescents converted (p=0.007). Importantly, 11 of the 12 converters were non-adherent to SGA treatment. Improvements in positive and negative symptoms were significant and similar in both treatment groups. It was concluded that that antidepressants may be advantageous over SGAs as a first-line treatment for patients at high risk for transitioning to psychosis, but interpretation was limited by non-random assignment and the widespread non-adherence to SGA treatment.

Non-pharmacological interventions have also been evaluated in youth at high risk for developing SZ. A double-blind trial randomized 81 patients at high risk for developing schizophrenia to 12-week treatment with 1.2 g/d of long chain omega-3 (LC*n*-3) fatty acids or placebo, followed by a 40-week observation period after treatment cessation (12 months total)[49]. By the end of the 12-month study, 2 of 41 individuals (4.9%) in the LC*n*-3 fatty acid arm and 11 of 40 (27.5%) in the placebo arm transitioned to threshold psychosis (p=0.007). During the 12-week treatment phase, LC*n*-3 fatty acids significantly reduced positive symptoms (p=0.01), negative symptoms (p=0.02), and general symptoms (p=0.01) and improved functioning (p=0.002) compared with placebo. The incidence of adverse effects did not differ between the treatment groups. It was concluded that LC*n*-3 fatty acids were safe and efficacious for preventing or delaying psychosis transitioning in high risk patients. A controlled trial randomized 58 patients at high risk for SZ to 6 months of

cognitive therapy or treatment as usual (TAU), and all patients were monitored for a total of 12 months [50]. By the end of the 12-month study, 2 of 35 (6%) patients in the cognitive therapy arm and 5 of 23 (22%) in the TAU arm had transitioned to threshold psychotic disorder (p=0.028). The likelihood of being prescribed antipsychotic medications was also significantly reduced in the cognitive therapy arm compared with TAU. These findings suggest the potential utility of LC*n*-3 fatty acids and/or cognitive therapy as safe and efficacious first-line interventions for patients at high risk for SZ.

High risk for bipolar disorder

The potential negative effects of antidepressant and psychostimulant medications in youth at high risk for developing BP have prompted studies investigating the efficacy and safety of mood-stabilizer and antipsychotic medications for the treatment of prodromal mood symptoms in high risk youth (Table 2). Lithium was evaluated for the treatment of MDD in 30 prepubertal children with a family history of BP (80%) or a multigenerational family history of MDD without BP (20%) in a 6-week double-blind placebo controlled trial. In this study, lithium (mean serum level: 0.99±0.16 mEq/l) was not more effective than placebo for treating prepubertal depression in these high-risk children [51]. A 12-week open-label study of divalproex for the treatment of 24 children and adolescents with at least one biological parent with BP and at least one of the following DSM-IV disorders: MDD, dysthymic disorder, cyclothymic disorder, or ADHD and moderate affective symptoms found that 75% of patients were responders by primary outcome criteria ("very much improved" or "much improved" on the Clinical Global Impressions-Improvement scale) [52]. However, a study of 56 youth ages 5 to 17 years with BP not otherwise specified (NOS) or cyclothymia who also had at least one biological parent with BP were randomly assigned to double-blind treatment with either divalproex or placebo for up to 5 years. The groups did not significantly differ in survival time for discontinuation for any reason (p=0.93) or discontinuation due to a mood event (p=0.55). Additionally, changes in mood symptom ratings and psychosocial functioning from baseline to study discontinuation did not differ between groups, suggesting that divalproex did not produce clinically meaningful improvements in this high risk population [53]. Thus, it is unclear whether divalproex ultimately will have a role in treating this population acutely or for prophylaxis of mood disorder progression.

A 12-week single-blind study investigated quetiapine for the treatment of 20 adolescents with mood disorder diagnoses other than mania who had a first-degree relative with BP [54]. It was found that 87% of patients were responders as defined by an endpoint Clinical Global Impressions-Improvement scale (CGI-I) score of “very much” or “much” improved. However, there was a statistically significant increase in body mass index, and over half (55%) of the patients experienced somnolence during the course of the study.

It is important to note that all of these early intervention trials for youth at high risk for BP evaluated relatively acute outcomes, and were not long enough to assess prevention of the development of mania. Thus, to date, there have been no prospective *prevention* trials using pharmacological interventions in children and adolescents at high risk for developing BP. However, Nadkarni and Fristad [55] found that multifamily psychoeducation groups exerted a protective effect on conversion to bipolar spectrum disorders among children with depressive spectrum disorders. Another one-year open trial found that family-focused therapy (FFT) with 13 children who had a parent with BP resulted in significant improvements in depression, hypomania, and psychosocial functioning scores [56]. In view of evidence for a protective effect of LC*n*-3 fatty acids in youth at high risk for developing psychosis [49], it is relevant that preliminary prospective intervention trials have found that LC*n*-3 fatty acids administered as monotherapy or adjunctively significantly reduce depression and/or manic symptom severity in pediatric and adolescent patients with MDD

[56] or BP [57,58]. These preliminary findings suggest that psychosocial therapy and/or LC*n*-3 fatty acids may represent candidate interventions for youth at high risk for developing BP, and warrant further evaluation in controlled trials.

CLINICAL VIGNETTE

'A.B.' is a 16 year old girl with a father with bipolar disorder who presented with several months of depressed mood, hypersomnia, anhedonia, fatigue, anergia, episodes of spontaneous crying and feelings of guilt and met *DSM-IV-TR* criteria for MDD. A.B. identified no precipitants for her depressive symptoms, denied significant anxiety symptoms or personal history of manic symptoms and generally described good family relationships and fair (but recently declining) academic performance at a local, parochial school. There was no prior history of manic symptoms, anxiety or ADHD. Additionally, there was no family history of antidepressant-induced manic symptoms in her mother or siblings. Citalopram was begun at a dose of 20 mg daily and after 5 weeks of treatment, A.B. had begun to improve but she still reported depressed mood and a moderate neurovegetative burden. To target her persistent depressed mood and neurovegetative symptoms, citalopram was increased to 30 mg daily. Three weeks after the increase in dose, A.B.'s mother reported concerns about her daughter's behavior, including her having been caught "sexting" several individuals with whom she had previously had superficial relationships and she had purchased several hundred dollars of clothing and lingerie at a local store. Additionally, A.B. required fewer than 4 hours of sleep per night, yet described her mood as "great" and reported racing thoughts, distractibility and that her family and friends had noticed that she was talking "faster." At that time, her mental status examination was remarkable for the wearing of excessive make-up, a low-cut shirt, pressured speech, psychomotor agitation, elated mood, and expanded affective range. Further, A.B.'s thought processes were tangential and thought content was remarkable for grandiosity and sexual preoccupation. Citalopram was discontinued and quetiapine was begun at 100 mg daily and titrated to 300 mg daily with resolution of the manic symptoms within 1 week.

This case illustrates the potential risk of antidepressant-induced manic symptoms (AIMS) in adolescents with a family history of bipolar disorder [26]. The emergence of manic symptoms occurred within several weeks of an increase in antidepressant dose and was not preceded by sub-syndromal manic symptoms. Additionally, this patient's course raises the possibility of that the use of a clinical staging model and alternative intervention (e.g., psychotherapy or LC*n*-3 fatty acids) may have obviated the need for an antidepressant as the first-line intervention. Importantly, and of relevance to clinicians encountering treatment-emergent manic in high risk youth who have been exposed to antidepressants, withdrawal of the SSRI and initiation of an SGA produced rapid, sustained improvement in manic symptoms. However, for less severe AIMS cases, it is possible that cessation of the antidepressant could be followed by close monitoring to see if manic symptoms abate naturally before antimanic medications are used. An alternate approach would have been to discuss the possibility of other medications with the family and patient, such as lamotrigine, quetiapine, or lithium. However, insufficient data exist to support the efficacy of these agents in depressed populations at high risk for BD, and future investigation should also include clinical and biological predictors of AIMS in youth.

CONCLUSIONS AND FUTURE DIRECTIONS

Early research efforts have begun to develop and validate criteria to identify individuals at high risk for developing BP and SZ, and to evaluate pharmacological and non-pharmacological interventions for the treatment of prodromal symptoms in high risk populations. While there have been some promising findings from early intervention trials

evaluating SGA medications, antidepressants, LC*n*-3 fatty acids, and cognitive-behavioral therapy in patients at high risk for developing psychosis, there is currently a dearth of prospective research in patients at high risk for developing mania. Indeed, the potential iatrogenic effects of antidepressant and psychostimulant medications, lack of efficacy of mood-stabilizer medications for prodromal mood symptoms, and adverse cardiometabolic effects associated with SGA medications highlight the urgent need to identify and evaluate evidence-based treatments for youth at high risk for BP. These findings further emphasize the need identify whether a patient is at high risk for developing mania or psychosis in order to exercise appropriate caution when prescribing 'standard of care' medications. Preliminary evidence endorses the adoption of a 'clinical staging' approach, and additional prospective research is warranted to evaluate the efficacy of candidate low risk first-line interventions, including psychosocial and/or LC*n*-3 fatty acids, in youth at high risk for developing BP or SZ.

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Key Points

- There have been some promising findings in evaluating SGA medications, antidepressants, LC*n*-3 fatty acids, and cognitive-behavioral therapy in patients at high risk for developing psychosis.
- Potential iatrogenic effects of antidepressant and psychostimulant medications, lack of efficacy of mood-stabilizer medications for prodromal mood symptoms, and adverse cardiometabolic effects associated with SGA medications highlight the urgent need to identify and evaluate evidence-based treatments for youth at high risk for BP.
- Preliminary evidence endorses the adoption of a 'clinical staging' approach for treating youth at risk for developing mania or psychosis, beginning with low risk firstline interventions, including psychosocial and/or LC*n*-3 fatty acids.

Table 1

Intervention trials in patients at high risk for developing psychosis

Study	Design	Interventions/Sample	Duration	Main Findings
McGorry et al. 2002	Randomized	Risperidone (RSP) 1–2 mg/d + CBT (n=31)	6 months	Transition rate: RSP+CBT: 36% vs. NBI: 10% (p=0.03)
	Single blind	Needs-Based Intervention (NBI, n=28)		Positive symptoms: RSP+CBT = NBI
				Negative symptoms: RSP+CBT = NBI
McGlashan et al. 2006	Randomized	Olanzapine (OLZ) 5–15 mg/d (n=31)	12 months	Transition rate: OLZ: 38% vs. Placebo: 16% (p=0.08)
	Double blind	Placebo (PLB, n=29)		Positive symptoms: OLZ > PLB
				Negative symptoms: OLZ = PLB
Yung et al. 2011	Randomized	RSP 0.5–2 mg/d + Cognitive Therapy (CT) (n=43)	6 months	Transition rate: RSP+CT: 4.7% vs. PLB+CT: 9.1% vs ST+PLB: 7.1% (p=0.92)
	Single blind	PLB + CT (n=44)		Positive symptoms: RSP+CT = PLB+CT = ST+PLB
		Supportive therapy (ST) + PLB (n=28)		Negative symptoms: RSP+CT = PLB+CT = ST+PLB
Cornblatt et al. 2007	Prospective	Antidepressants (AD, n=20)	6 months	Transition rate: AD: 0% vs. SGA: 38% (p=0.007)
	Naturalistic	SGA antipsychotics (n=28)		Positive symptoms: AD = SGA
				Negative symptoms: AD = SGA
Amminger et al. 2010	Randomized	LC*n* -3 fatty acids (1.2 g/d) (n=40)	12 weeks	Transition rate: LC*n* -3: 4.9% vs. PLB: 27.5% (p=0.007)
	Double blind	Placebo (n=41)		Positive symptoms: LC*n* -3 > PLB
				Negative symptoms: LC*n* -3 > PLB
Morrison et al. 2004	Randomized	Cognitive therapry (CT, n=35)	6 months	Transition rate: CT: 6% vs. TAU: 22% (p=0.03)
	Single blind	Treatment as usual (TAU, n=23)		Positive symptoms: CT > TAU
				Negative symptoms: Not reported

Table 2

Intervention trials in patients at high risk for developing mania

Study	Design	Intervention	Target Dose	Duration	Findings
Geller et al. 1998	Randomized	Lithium (n=17)	Serum 0.9–1.3 mEq/l	6 weeks	C-GAS: Lithium = Placebo
	Double blind	Placebo (n=13)			
Chang et al. 2003	Open-label	Divalproex (n=24)	15–20 mg/kg/d	12 weeks	↓ CGI-I, ↓ HAM-D, ↓ YMRS
Findling et al. 2007	Randomized	Divalproex (n=29)	10 mg/kg/d	<60 months	CGAS: Divalproex = Placebo
	Double blind	Placebo (n=27)			YMRS: Divalproex = Placebo
					CDRS-R: Divalproex = Placebo
DelBello et al. 2007	Single blind	Quetiapine (n=20)	300–600 mg/d	12 weeks	CGI-I: Quetiapine > Placebo
					YMRS: Quetiapine > Placebo
					CDRS-R: Quetiapine > Placebo
Milkowitz et al. 2011	Open	Family-focussed therapy (n=13)	3 Sessions/month	4 months	↓ CDRS-R, ↓ YMRS

C-GAS, Children's Global Assessment Scale
CGI-I, Clinical Global Impressions-Improvement
YMRS, Young Mania Rating Scale
HAM-D, Hamilton Rating Scale for Depression
CDRS-R, Children's Depression Rating Scale-Revised