Published in final edited form as:
Dev Psychopathol. 2008 ; 20(3): 881–897.

Prevention of Bipolar Disorder in At-Risk Children: Theoretical Assumptions and Empirical Foundations

David J. Miklowitz and
University of Colorado, Boulder

Kiki D. Chang
Stanford University School of Medicine

Abstract

This article examines how bipolar symptoms emerge during development, and the potential role of psychosocial and pharmacological interventions in the prevention of the onset of the disorder. Early signs of bipolarity can be observed among children of bipolar parents and often take the form of subsyndromal presentations (e.g., mood lability, episodic elation or irritability, depression, inattention, and psychosocial impairment). However, many of these early presentations are diagnostically nonspecific. The few studies that have followed at-risk youth into adulthood find developmental discontinuities from childhood to adulthood. Biological markers (e.g., amygdalar volume) may ultimately increase our accuracy in identifying children who later develop bipolar I disorder, but few such markers have been identified. Stress, in the form of childhood adversity or highly conflictual families, is not a diagnostically-specific causal agent but does place genetically and biologically vulnerable individuals at risk for a more pernicious course of illness. A preventative family-focused treatment for children with (a) at least one first-degree relative with bipolar disorder, and (b) subsyndromal signs of bipolar disorder, is described. This model attempts to address the multiple interactions of psychosocial and biological risk factors in the onset and course of bipolar disorder.

Keywords

expressed emotion; high-risk study; subsyndromal; prevention; family-focused treatment; early intervention

INTRODUCTION

Bipolar disorder (BD) in childhood and adolescence is much more common than once thought. In a recent study of 642 adults with bipolar disorder, 50%–66% reported that their onset was prior to age 18, and 15%–28% before 13 (Perlis et al., 2004). A study of the Amish population found that between 10%–20% of adults reported the onset of symptoms before age 10 (Egeland, Hostetter, Pauls, & Sussex, 2000; Lish, Dime-Meenan, Whybrow, Price, & Hirschfeld, 1994). The recent large-scale National Comorbidity Survey-Revised found that about 2% of the population has bipolar I or II disorder, and another 2.4% has subsyndromal forms of the disorder within the bipolar spectrum (Merikangas et al., 2007). Rates among bipolar children and adolescents are lower but still significant (1%–2% in most studies, depending on the ascertainment method; Lewinsohn, Klein, & Seeley, 2000; Verhulst, van der Ende, Ferdinand, & Kasius, 1997). In referred clinic samples, the rates vary from 0.6% – 15% (Pavuluri, Birmaher, & Naylor, 2005). There have been dramatic increases (by one estimate, 40-fold) in the diagnosis of pediatric bipolar disorder in community settings within the past 10 years,

leading some to question the reliability and validity of the diagnosis in clinical practice (Moreno et al., 2007).

Although the average age at illness onset is 18 yrs in epidemiological samples (e.g., Merikangas et al., 2007), the onset of subsyndromal symptoms is much earlier. For example, Egeland and coworkers (1987, 2000) observed that in the Amish population, subsyndromal affective symptoms (for example, hypersensitivity, anger dyscontrol, episodic mood lability) were observable at least 9–12 years before the illness was diagnosed.

Longitudinal studies have repeatedly documented the highly recurrent course of child- and adult bipolar disorder, its significant impact on functioning and quality of life, and its high association with suicide as an eventual outcome (Birmaher et al., 2006; Coryell et al., 1993; Isometsa, 1993; Suppes et al., 2001). Before the onset of the full syndrome, youth with a family history of bipolar disorder often experience subsyndromal mood swings. If untreated, these "prodromal" youths often develop comorbid disorders such as substance or alcohol abuse or anxiety disorders and various levels of psychosocial or academic impairment. When they are eventually treated, it is often with antidepressants or psychostimulants instead of mood stabilizers or atypical antipsychotics, which may increase their risk of manic onset (Altshuler et al., 1995; Leverich et al., 2007;).

Given the high prevalence and damaging effects of early-onset bipolar illness, researchers need to more systematically elucidate the developmental pathways to the disorder and evaluate the effectiveness of early interventions. A young population should be targeted for early identification and intervention because of the window of opportunity represented by the short prodromal period before the fully debilitating syndrome begins.

This article addresses a key set of questions from the perspective of developmental psychopathology: how do bipolar symptoms emerge during development in the context of different risk and protective factors in the social, emotional, cultural, cognitive, biological, or familial domains (Cicchetti & Toth, 1998)? Are there developmental organizations of systems that place an individual at risk for the illness? What are the various components of this disorganization, and are they amenable to intervention? In addressing these themes, we pose several subsidiary questions: (1) what is known about early signs of mood or behavioral disturbance in children who are at risk for bipolar disorder by virtue of family history? (2) What symptoms appear to "hang together" as a unique syndrome defining risk? (3) Which genetic, neuroanatomical, neurophysiological or environmental variables place children at additional risk to develop bipolar disorder onset or recurrences, and which factors are compensatory when potentiating factors are present? The disorder clearly has a genetic basis, but genetic vulnerability only translates into phenotypic expression in a minority of cases (Smoller & Finn, 2003). Possibly, biological markers of risk will increase the predictive accuracy of measurable genetic vulnerabilities to the disorder.

As an example of a neuroanatomical marker, the size of the amygdala is smaller than average in bipolar children and larger than average in bipolar adults, suggesting that the disorder may be associated with abnormal amygdalar development (DelBello, 2006). As an example of an environmental potentiator, early sexual abuse is associated with an earlier age at onset of bipolar disorder, a greater frequency of comorbidity, more suicidal thinking, and more treatment resistance (Leverich et al., 2002).

Finally, (4) what kinds of early interventions might serve a protective function in delaying the onset of the disorder or minimizing its severity, and whom would we target for such interventions? What variables in the social, emotional, interpersonal, genetic, biological, or cultural domains should be the hypothesized mediators to determine whether early interventions are successful? Like depression, there are multiple causal pathways to an early

onset of bipolar disorder, and multiple patterns of individual adaptation, some of which may be amenable to alteration through psychosocial interventions. In turn, what we learn from prevention trials may inform our understanding of risk mechanisms that initiate or maintain the disorder (Garber, 2006).

EQUIFINALITY AND MULTIFINALITY

In reviewing the literature on risk for bipolar disorder, we must keep in mind two principles of developmental psychopathology: equifinality and multifinality. *Equifinality*, the process by which multiple developmental pathways converge on the same phenotypic outcome, complicates efforts towards creating truly homogenous biologically-based groupings based on external behaviors (Cicchetti & Rogosch, 1999). The diagnosis of bipolar disorder in late childhood or early adulthood – even when strictly defined - is probably the end result of a number of different pathways affected by genetic variables, environmental variables, gene by environment interactions, and other risk and protective processes at different phases of development. Both genetic and non-genetic factors clearly play a role in the disorder, given that concordance rates between identical twins range from 40–97% depending on the definition of BD (Alda, 1997; Hasler, Drevets, Gould, Gottesman, & Manji, 2006).

An implication of the equifinality concept is that the search for uniform risk factors (for example, single genes) common to all presentations of the illness is likely to fail. The accuracy of predicting "caseness" is likely to be improved by examining gene by environment interactions and how these change across the lifespan, as well as the moderating effects of psychological processes such as coping skills or self-esteem.

Multifinality creates further heterogeneity in pediatric bipolar samples because individuals with the disorder are affected to different degrees. Different constellations of risk and protective factors result in a dispersion of symptomatic and functional outcomes over the lifespan of the individual. The principle of multifinality operates when considering the outcome of children diagnosed with "prodromal" bipolar disorder, which may or may not eventuate in development of the full bipolar I syndrome (e.g., Lewinsohn et al., 2000).

As an example of the concept of multifinality, consider the role of high expressed emotion (EE) attitudes in parents (high levels of criticism, hostility, or emotional overinvolvement as expressed during an interview) and their relations to the symptomatic outcomes of BD adults and adolescents over 1–2 year periods (Miklowitz, Biuckians, & Richards, 2006; Miklowitz, Goldstein, Nuechterlein, Snyder, & Mintz, 1988; Miklowitz, Richards, George, Suddath, & Wendel, 2000; O'Connell, Mayo, Flatow, Cuthbertson, & O'Brien, 1991; Yan, Hammen, Cohen, Daley, & Henry, 2004;). Parental EE attitudes are correlated differently with age at onset in boys versus girls, such that parents express more criticisms toward childhood-onset boys and adolescent-onset girls (Coville, Miklowitz, Taylor, & Low, in press). In addition, the degree to which parental EE attitudes are associated with later recurrences of bipolar disorder may be moderated by variables such as the intactness of the biological family unit or the degree to which EE attitudes are expressed in verbal interactions between the parent and offspring (Geller et al., 2004; Miklowitz et al., 1988). Thus, the same context (a high EE environment) may eventuate in a wide dispersion of outcomes depending on the range of moderating and mediating variables in the social, biological, or cultural context. The concepts of equifinality and multifinality will be revisited in later sections of this review.

GENETIC ORIGINS OF BIPOLAR DISORDER

How do we know which children will later develop bipolar disorder? Twin and family studies report that the disorder has a 59–87% heritability, and first-degree relatives of probands with BD are at very high risk of BD themselves (Smoller & Finn, 2003). Concordance rates among

identical twins average 57%, and among dizygotic twins, 14% (Alda, 1997). Averaging across studies, and using the narrow DSM-IV criteria for bipolar I or II disorder, the morbid risk of major affective disorder to first degree relatives if an individual has bipolar disorder is about 23% (about 9% bipolar and 14% major depressive disorder) (Smoller & Finn, 2003). Familial rates are higher when one includes the spectrum conditions. Notably, the risk of bipolar spectrum disorders in the offspring of parents with BD I or II disorder ranges from 14% to 50% across studies, and the risk of major depressive disorder ranges from 7% to 43% (Chang, Steiner, & Ketter, 2003).

These numbers, while confirming the role of genetic transmission, point to the existence of numerous risk and protective factors in moderating the appearance of bipolar disorder in at-risk children. The majority of children with first-degree bipolar relatives do *not* develop bipolar disorder (multifinality).

Whereas twin and family studies support the position that bipolar disorder has genetic roots, they tell us little about the nature of its origins. As Kendler (2005) explains, evidence from twin, adoption, and family studies only show that "genes that affect risk for these disorders must exist somewhere on the human genome (pp. 1248)." In all likelihood, bipolar disorder will be associated with the cumulative effects of numerous genes of small effect (none of which code directly for the illness) and which interact with different contextual factors. Nonetheless, multiple loci have been identified in linkage studies (Mathews & Reus, 2003).

EVIDENCE FOR MOOD AND BEHAVIOR DISTURBANCE IN AT-RISK CHILDREN

When a child has a first-degree relative with bipolar I or II disorder, what mood or behavioral risk indicators increase the likelihood that the child will develop bipolar disorder, or at least that developmental continuities will be observed from youth to adulthood? First, various internalizing or externalizing disorders appear with high frequency in genetically susceptible samples. A meta-analysis of studies conducted before 1997 found that offspring of bipolar parents 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 (LaPalme, Hodgins, & LaRoche, 1997). Between 50% and 60% of the offspring of BD parents have some type of psychiatric disorder, especially mood, anxiety, and disruptive behavior disorders (Carlson & Weintraub, 1993; Chang et al., 2000; Chang et al., 2003; Wals et al., 2005).

The risk to offspring is also observed cross-culturally. A Turkish study examined the prevalence of mood and disruptive behavior disorders in 35 children of 29 adult outpatients with a DSM-IV diagnosis of bipolar I disorder, compared with 33 children of 29 healthy adults (Emiroglu, Ozerdem, Miklowitz, Baykara, & Akay, in press). The offspring of bipolar patients had a 9.48 fold higher risk of receiving a psychiatric diagnosis than the controls. Only two children of patients with bipolar disorder were diagnosed with a mood disorder, but 30.9% displayed mild depressed mood, compared with 8.8% of the controls. The bipolar offspring also scored significantly higher on the hyperactivity and conduct problems subscales as well as the ADHD index of the Conners' Teacher Rating Scale.

From the perspective of risk computation, the children of parents with BD are the most relevant population in which to implement early interventions. The presence of mood or behavioral disturbance increases the likelihood of identifying "true positive" cases. However, aiming an early intervention at all children of bipolar parents who show mood disturbance would lead to an unacceptable number of unnecessary treatments, because the majority of these children will not develop the disorder. Thus, researchers must go a step farther and examined putative

markers that moderate risk among children who are genetically predisposed to bipolar disorder. Knowledge of these markers would make early intervention programs more cost-effective.

DEFINING THE INITIAL SYMPTOM PRESENTATION

Risk markers can take a variety of forms, although they do not necessarily tell us how individuals develop the disorder (risk mechanisms). At the simplest level are subsyndromal forms of the disorder, such as early cyclothymic cycling patterns, or the presence of disorders that are often comorbid with BD (for example, ADHD). Some investigators have examined the constellation of symptoms that predates the first onset of BD and distinguishes it from the onset of other psychiatric disorders when a family history of bipolar disorder is also present.

Studies of Bipolar Disorder Not Otherwise Specified (BD-NOS) and Cyclothymia

A group of children who are theoretically at the highest risk for developing BD are those who, in addition to having have an immediate family history of bipolar disorder, have significant symptoms of depression and mania that do not meet full criteria for BD I or II. Retrospective studies have found that BD commonly begins with subsyndromal mood symptoms (depression, mania, suicidality; Lish et al., 1994). For example, a child may have periods of significant irritability plus three associated manic symptoms that may not last an entire week, but instead last for 4 hours on 2 consecutive days. These youths are commonly diagnosed with BD "not otherwise specified" (BD-NOS) if they are significantly impaired by their symptoms (Carlson et al., 2003; NIMH, 2001).

A cross-sectional study with a large sample (N = 400) of children aged 5–17 yrs clarified the nature of this high-risk phenotype (Findling et al., 2005). Children of bipolar parents were more likely to have symptoms of mania or hypomania than were children without a bipolar parent, but were not at higher risk for ADHD or disruptive behavior disorders than children without a bipolar parent. The combination of elevated mood with irritability, rapid mood fluctuations, and psychosocial dysfunction identified a high-risk group which the authors referred to as 'cyclotaxic.'

A similar cluster of prodromal behaviors was identified by Egeland et al. (2000, 2003; Shaw, Egeland, Endicott, Allen, & Hostetter, 2005) in a 7–10 year follow-up of Amish children. Few of the children of bipolar I or II parents actually developed bipolar disorder within the time frame. Compared to children without a bipolar parent, children with a bipolar parent were distinguished at the 7- and 10-year follow-up by episodic mood lability, anxiousness, hyper-alertness, distractibility, easy excitability, school role impairment, somatic complaints, and "stubborness." With 3 years of additional follow-up, features that distinguished the groups included fewer internalizing and more externalizing "manic-like" behaviors including high energy, sleep disturbances, excessive and loud talking, and problems with thinking and concentration. Many of these features, of course, are key features of ADHD as well as bipolar disorder. Thus, the diagnostic specificity of early bipolar spectrum symptoms is still in question.

Longitudinal Studies

What early symptomatic states have developmental continuity and are longitudinally associated with adult bipolar disorder? A 2-year prospective study in France examined 80 children and adolescents (7 – 17 yrs) with DSM-IV major depressive disorder (Kochman et al., 2005). Of the 80, 35 (43%) converted to bipolar I or II disorder within 2 years. Youths with cyclothymic temperaments (n = 47) were highly likely (64%) to experience at least one full blown hypomanic or manic episode within 2 years, as compared to only 15% of youths without cyclothymic temperaments (n=33). The cyclothymic children also had more depressive

episodes at follow-up, more psychotic symptoms, more suicidal ideation and attempts, and more instances of antidepressant-induced hypomanic or manic episodes. Cyclothymic children were described, at baseline, as highly mood-labile and emotionally overactive, explosively angry, impulsive, aggressive, and emotionally hypersensitive, much as the studies by Findling et al (2005) and Egeland et al (2000, 2003) had described. Young adults with these cyclothymic temperaments have been found to have a high familial loading for affective disorder (Akiskal, 1995). The Kochman et al. study, while underscoring the validity of cyclothymia as a prodromal manifestation of bipolar disorder, also illustrates the diverse outcomes of children initially diagnosed with major depressive disorder (multifinality).

Lewinsohn and colleagues (2000, 2003) at the Oregon Research Institute conducted one of the few longitudinal high-risk studies of bipolar disorder. Cases were chosen based on positive responses of high school students to a structured diagnostic interview. A follow-up into young adulthood of the adolescents who had a narrow bipolar phenotype (at least one clear-cut manic episode) revealed continuity of the narrow phenotype with bipolar disorder in young adulthood, although not in every case. Interestingly, a much broader phenotype (defined as meeting the 'A' criteria but not the 'B' criteria by DSM-III-R) was more often associated with major depressive disorder in adulthood than with bipolar illness. This study is limited by its sole reliance on adolescent instead of parental report. The results may generalize to community high school student samples but not necessarily to clinical samples.

The findings of the Course and Outcome in Bipolar Youth (COBY) study most clearly document that children with well-defined BD-NOS and a first-degree relative with BD are at high-risk to progress to BD I or II disorder (Birmaher et al., 2006). A total of 131 children were identified with BD-NOS, defined as a distinct period of abnormally elevated, expansive or irritable mood plus two (three if irritable mood only) DSM-IV symptoms of mania that caused a change in functioning, lasted for at least one day, and were present for a total of at least four days in a child's lifetime. Children with BD-NOS were at significant risk for switching to BD I (14.5%) or II (9.2%) over 22 months, with the highest rates among those children with a first- or second-degree relative with mania or hypomania (30.6% versus 17.4%). Children with BD-NOS were also at high risk for a variety of adverse outcomes at follow-up, including rapid mood changes, suicidality, and psychosocial dysfunction. In fact, children with BD-NOS took longer to achieve remission and had more weeks with subsyndromal manic or depressive symptoms than children with BD I disorder (Birmaher et al., 2006). Interestingly, even though the BD-NOS children fell short of the diagnostic criteria for the full bipolar syndrome, they did not differ from BD I or II children in the number or type of medications given by community practitioners.

A related question is whether moods that dramatically fluctuate from a euthymic baseline to a severely high or low mood are pathognomonic for developing BD. Some investigators, however, have argued that children with bipolar disorder can have non-episodic, chronic mania and irritability (Biederman et al., 2003). More generally, there is disagreement among researchers as to what constitutes an episode (Tillman et al, 2004).

Leibenluft, Cohen, Gorrindo, Brook, & Pine (2006) analyzed data from the longitudinal Smoky Mountain Youth study which, while not a study of bipolar disorder, had a considerable sample size assessed with multi-informant structured diagnostic interviews. 776 youth were evaluated at three time points: mean age 13.8, mean age 16.2, and mean age 22.1. The best predictor of mania onset at both time 2 and time 3 was episodic irritability at time 1. Depression in early adolescence also predicted later mania onset. Interestingly, chronic, non-episodic irritability predicted later onset of ADHD and major depression, but not mania, a result which parallels the Lewinsohn et al. study. Thus, episodicity of mood symptoms seems an important variable to consider in defining risk.

The Prodrome to Mania and Depression

Two studies have retrospectively focused on the prodrome to first onsets of mania or hypomania. A retrospective study of 34 bipolar youths (Correll et al., 2006; Correll et al., 2007) revealed that a lengthy symptomatic prodrome often precedes the first episode of full mania. When defining prodromes as 3 or more manic symptoms of moderate severity or greater, which is subthreshold for DSM-IV mania, the mean manic prodrome duration was 10.8 ± 14.7 mos. For most of the youths, the onset was slow with gradual deterioration (58.8%) or slow with quick worsening (29.4%) rather than rapid (11.8%). The most common prodromal features of subsequent manic episodes were a drop in school functioning (69%), irritability (59%), racing thoughts (59%), and mood swings (57%).

The most reliable symptom complex predating mania is depression. In a study of children (mean age 10.3 yrs) with prepubertal major depressive disorder, Geller, Zimerman, Williams, Bolhofner, & Craney (2001) found that 33% had developed bipolar I disorder by a 10-year follow-up, compared to none of a group of age-matched healthy controls. In a 5-year prospective study of 129 children of bipolar parents in the Netherlands, 12 of the 13 offspring who developed hypomania at follow-up had had a major depressive episode an average of 5 years earlier (Hillegers et al., 2005). However, childhood depression is associated with a multifinality of outcomes in adulthood (Cicchetti & Toth, 1998). In the Geller study, high rates of major depressive disorder (36%) and substance abuse disorders (31%) were also observed in young adulthood. Thus, the utility of depression as a risk factor in the absence of other risk factors (e.g., family history of bipolar disorder; mood cyclicity) is probably minimal.

ADHD as an Early Risk Indicator

A more controversial question is whether ADHD is a harbinger of the later development of BD among genetically at-risk children. Because ADHD generally has an earlier age at onset, ADHD symptoms may reflect an early manifestation of bipolar disorder (or perhaps a developmentally-specific phenotype) in some children (Singh, DelBello, Kowatch, & Strakowski, 2006). In this view, ADHD reflects the same “molar organization” that mania reflects in adulthood: hyperactive behavior, inattention, impulsiveness, irritability, distractibility, and excessively goal-driven behaviors. ADHD generally has an earlier onset than BD, making its appearance in the context of a positive family history of bipolar disorder a potentially fruitful way of identifying high-risk youths.

Bipolar patients retrospectively report high rates of ADHD symptoms as children, and often report that inattention was their first symptom (e.g., Lish et al., 1994). Virtually every study finds a high rate of comorbidity between childhood BD and ADHD (Chang et al., 2003; Fergus et al., 2003; Geller, Warner, Williams, & Zimerman, 1998; Perlis et al., 2004;). The significance of this overlap is uncertain, however. One view is that the psychostimulants used to treat ADHD increase the likelihood that mania will appear earlier in high-risk children. A study in the Netherlands found only 1/6th the rate of bipolar disorder in prepubertal children that is reported in the U.S.; the authors attributed this difference in prevalence to the lower use of stimulants in the Netherlands (Reichart & Nolen, 2004). However, in a 6-year follow-up of U.S. children (average age 9.7) with ADHD, 29% “switched” to bipolar I disorder by average age 16, but those who switched were *less* likely to have been treated with stimulants (Tillman & Geller, 2006). Other predictors of switching included a paternal family history of recurrent depression and high psychosocial impairment.

The issue of overlapping diagnostic criteria has not been resolved, although several studies find that there is a high rate of comorbidity between bipolar disorder and ADHD even when overlapping symptom criteria (e.g., increased energy) are removed from consideration (Kim & Miklowitz, 2002). Finally, the high rate of ADHD in the family pedigrees of bipolar children

suggests a degree of overlap in the genetic etiology of the two conditions (Faraone et al., 1997). Brain areas involved with mood regulation overlap with attentional circuitry (i.e., the dorsolateral prefrontal cortex, anterior cingulate cortex, and striatum). Disruptions in these areas and connections between them could lead to disruption of mood regulation and attention.

Summary

The emerging evidence suggests that certain symptomatic constellations are prodromal risk indicators for the onset of BD I or II later in childhood or in early adulthood. Children at highest risk for developing bipolar disorder have a first-degree relative with BD and (1) a subsyndromal form of BD (BD-NOS or cyclothymic disorder), (2) fully syndromal DSM-IV major depressive episode with a history of significant but subsyndromal manic symptoms, or (3) possibly, ADHD with mood fluctuation. All three risk definitions require that the child show evidence of cyclicity of symptoms (return to baseline or to another mood state following the offset of subsyndromal manic or depressive symptoms). However, this literature is limited by the small number of long-term follow-up studies into adulthood. Thus, we cannot say for certain whether the clinical presentations observed in youth are truly pre-bipolar syndromes or time-limited "phenocopies." Ongoing interactions between individual genotypes and environmental-contextual factors in the transition to adolescence or early adulthood are likely to lead to a diversity of outcomes among youth with similar prodromal presentations.

NEUROBIOLOGICAL MARKERS OF RISK

Neurobiological risk markers for bipolar disorder would serve many functions: (1) to aid in more precise diagnosis of bipolar spectrum disorders, (2) to shed light on the etiology of BD, and (3) to aid in detection and quantification of risk for BD development. While biological studies of BD have revealed genes and brain regions thought to be involved with the pathophysiology of the disorder, no single or combination of such biological findings has been found to be specific to or predictive of a bipolar diagnosis. Therefore, future use of genetic or biological markers will be dependent on understanding the relative degree of contribution from many different biological risk processes. Based on prior research, these may include amygdalar size, prefrontal activation in response to affective stress, and the short-allele of the 5-HTTLPR gene (Chang, Howe, Gallelli, & Miklowitz, 2006). Understanding the cumulative effects and interactions among different neuropathophsiological factors may help us to tailor preventative interventions.

Our current understanding regarding the neuropathophysiology of BD centers on disruption in circuitry within the prefrontal-limbic network (Phillips, 2006; Strakowski, 2005;). For example, certain abnormalities in the limbic system -such as altered amygdalar structure and functionality - could exist early in childhood in at-risk individuals, whether inborn or due to excessive neuronal pruning/apoptosis during childhood and adolescence (Blumberg et al., 2004; Chang et al., 2006; Karchemskiy et al., under review). Further disruptions in the network, particularly in prefrontal regions, may develop with continuing mood episodes, stress, and or exogenous substances such as alcohol. Neurovegetative symptoms, including changes in sleep, appetite, and energy, associated with BD are hypothesized to result from the effects of dysregulated anterior limbic network activity on hypothalamic nuclei (Strakowski, Delbello, & Adler, 2005).

This model of BD development is supported by neuroimaging studies in pediatric BD, which find abnormalities in subcortical-limbic brain regions, especially in the amygdala and basal ganglia (Caetano et al., 2005; Chang et al., 2006; Karchemskiy et al., under review). Whereas studies in adults with BD have reported increased, decreased, or unchanged amygdalar volume, studies in pediatric BD have been more consistent in finding relatively decreased amygdalar volume (DelBello, 2006). This decreased volume may mean a heightened activity in the

amygdala in response to affective stress, as demonstrated in functional imaging studies in healthy adults (Yurgelon-Todd et al., 2004) as well as children with BD (Rich et al., 2006). Theoretically, such heightened activation without compensatory prefrontal regulation could lead to a heightened experience of mood states (euphoria or sadness), that could then continue to a fully syndromal mood episode. Preventive interventions geared toward decreasing limbic hyperactivity might serve to prevent mood episodes and the development of full mania.

The prefrontal cortex (PFC) also represents a useful target when considering preventative interventions. The PFC likely suffers neurodegeneration with prolonged bipolar illness (Strakowski et al., 2002; Rajkowska, Halaris, & Selemon, 2001; Gallelli et al., 2005; Manji & Duman, 2001). Stress from repeated mood episodes has been postulated to be causal to this process (Hashimoto, Shimizu, & Iyo, 2004; Rajkowska, 2000), leading to less prefrontal mood regulation and greater cycling and treatment resistance (Chang et al., 2004). This model fits the theory of kindling as applied to the progression of affective disorders (Post, 1992). Kindling refers to the process where the combination of psychosocial stress and genetic vulnerability gradually leads to a full mood episode, after which stress plays a decreasing role in triggering recurrences until episodes occur autonomously. Interventions early in the course of kindling may reverse this course. For example, in animal studies, rats given sodium valproate prior to onset of electrical stimulation will not develop seizures (Post, 2002).

The developing juvenile brain may be especially susceptible to neuronal cell loss with repeated manic episodes (Chang et al., 2004; Kochman et al., 2005). Thus, an intervention that decreases stress and improves cognitive control of mood could have a combined effect on preserving prefrontal function and neuronal integrity. Furthermore, pharmacologic or psychotherapeutic interventions which prevent excessive substance abuse and promote adherence to mood stabilizer regimens may prevent neurotoxicity in subsceptible areas (such as the PFC and hippocampus). Much needs to be done, however, to specify the components of these interventions, the neural circuitry they are targeting, and when in the development of the disorder they will have their optimal preventative effects.

THE ROLE OF STRESS AND EARLY ADVERSITY IN ILLNESS ONSET AND RECURRENCES

As indicated earlier, bipolar disorder can be conceptualized as a heterogeneous condition that is the result of many different developmental trajectories. These trajectories comprise interactions of the genetic, biological, social, familial, and cultural systems at different points of development. Among these systems, early adversity appears to moderate risk for a negative course of mood disorder, especially among genetically predisposed persons.

In considering the role of stress and adversity, one must consider the backdrop against which these factors operate. Tilman and Geller (2003) reported that preadolescent and early adolescent bipolar children had more independent and dependent life events than healthy controls. Although the social alienation associated bipolar disorder may increase the likelihood of dependent negative life events (for example, peer rejection), the cause of the greater occurrence of independent events is less clear. Possibly, the increased incidence of mood disorders in the child's family makes the child more likely to be exposed to events beyond his or her control. The occurrence of uncontrolled stressful events may account in part for the high rates of anxiety comorbidity observed among childhood bipolar patients (e.g., Masi et al., 2004).

Studies of Early Adversity and Family Conflict

Dienes, Hammen, Henry, Cohen, & Daley (2006), in a study of 58 bipolar I adults evaluated every 3 months for one year, found that childhood adversity moderated the association between life stress and recurrence among bipolar adults. Patients with more severe early adversity (particularly sexual abuse and parental neglect, but not physical abuse) had earlier ages at onset and reported lower levels of stress prior to new episodes than patients with less severe early adversity. These findings, although based on adults, suggest that some early-onset bipolar patients are more reactive to stress due to preexisting vulnerablities (Hammen & Gitlin, 1997).

In a large-scale longitudinal study of adult bipolar disorder, Post & Leverich (2001) reported that early age at illness onset was associated with sexual abuse in childhood and adolescence. Abuse and earlier illness onset were associated with more impairments in social, educational and occupational functioning, a worse course of bipolar illness, more suicidal thinking and attempts, more illness comorbidity (notably axis II), and a poorer response to pharmacological treatments in adulthood. It is not clear from this correlational research whether adversity is a direct cause of poor outcomes of bipolar illness, or indeed whether it plays a causal role in the disorder's onset. It may be part of a larger developmental pathway. Notably, early adversity may mediate the relationship between genetic vulnerability and early onset of the illness, which in turn may predict a less favorable prognosis.

Miklowitz, Biuckians, & Richards (2006) found an association between highly critical EE attitudes among parents of bipolar teenagers and a more deteriorative course of illness over two years in a treatment program. Parents expressed more highly critical attitudes toward girls, especially those with adolescent onset (Coville, Miklowitz, Taylor, & Low, under review). Geller, Tillman, Craney, & Bolhofner (2004) found that low ratings of maternal warmth were associated with earlier recurrences over four years among childhood and preadoleescent bipolar patients.

By what mechanisms would adversity or family conflict influence the onset or course of bipolar illness? Among children who are genetically and neurobiologically at risk for bipolar disorder, emotional, physical, or sexual abuse or severe, ongoing family conflict may interfere with the development of secure attachment relationships, emotional self-regulation skills, modulation of arousal and attention, and the development of a coherent self-organization (Cicchetti & Toth, 1998). Parents who themselves have mood disorders are likely to confer risk to their offspring via environmental-psychosocial as well as genetic mechanisms. In particular, the self-critical styles of depressed parents can be transmitted to infants in the form of negative affect and low acknowledgment of infant agency, which may interfere with cognitive and emotional development (Cicchetti & Toth, 1998; Murray, Kempton, Woolgar, & Hooper, 1993).

The early experiences of adversity are likely to make transitions to subsequent developmental challenges more difficult. Thus, high levels of adversity are a potentiating factor that should be considered when identifying high risk samples and designing preventive interventions.

HOW MIGHT PREVENTIVE INTERVENTIONS PROCEED?

The foregoing sections have made the case that risk for bipolar disorder is genetically mediated and can often be observed as subsyndromal signs of the illness. Moreover, the interpersonal and family stress associated with the development of symptoms – both the stress caused by the symptoms and uncontrollable stressors or adversity that interferes with the child's successful developmental adaptation – may interfere with prefrontally-mediated mood regulation. In turn, poor emotional self-regulation may be associated with increased cycling and greater resistance to pharmacologic interventions. Thus, preventive interventions (i.e., those administered before the first fully syndromal manic episode) that alleviate early symptoms, enhance the ability to

cope with dependent and independent stressors, and restore healthy prefrontal neural circuitry should reduce the likelihood of adverse outcomes of the disorder (Chang et al., 2006). With these assumptions, the researcher or clinician planning interventions could intervene at the level of biological markers (e.g., brain-derived neurotrophic growth factor), environmental stressors (e.g., aversive family interactions), or subsyndromal mood or ADHD symptoms.

Some early interventions are likely to be pharmacological and aimed at decreasing biological vulnerabilities (Post & Leverich, 2006). Several studies have examined the impact of pharmacotherapy on the early course of symptoms among children at risk.

Pharmacotherapy for Treating Mood Symptoms in High-Risk Cohorts

Three pharmacological studies have been conducted with youths at risk for bipolar disorder. Chang et al. (2003) provided open treatment with divalproex for 24 children (average 11.3 years) with a first-degree relative with BD. The youths were diagnosed with major depressive disorder, cyclothymic disorder, dysthymic disorder, or ADHD, and had at least moderate current affective symptoms. All youths were treated with divalproex for 12 weeks with careful dosage titration to achieve therapeutic serum levels. Of the 23 who completed the trial, 18 (78%) were considered “very much improved” or “much improved.” This study provides evidence for the utility of pharmacological intervention for youths with two risk markers (a first degree relative with BD and current mood disorder symptoms), but in the absence of a randomly assigned placebo group, it is impossible to determine whether symptoms would have stabilized with time.

A similar conclusion was drawn by DelBello, Adler, Whitsel, Stanford, & Strakowski (2007) using quetiapine. Twenty adolescents who had at least one bipolar first-degree relative, a DSM-IV diagnosis of bipolar NOS, bipolar II, or dysthymia/major depression, and active mood symptoms were given quetiapine for 12 weeks. 87% of the subjects responded at week 12, with reductions observed on the Young Mania Rating Scale and the Child Depression Rating Scale.

Only one study has examined the effectiveness of pharmacotherapy in a randomized, placebo-controlled design. Findling et al. (2005) recruited 56 youths who averaged 10.7 years, met DSM-IV criteria for BD-NOS or cyclothymia, and had at least one biological parent with bipolar disorder. The youths were randomly assigned to divalproex monotherapy or placebo and followed for up to 5 years. The groups did not differ in survival time to medication discontinuation (the primary study outcome variable) or discontinuation due to a “mood event.” Both groups improved over time in mood and psychosocial functioning, suggesting that subsyndromal symptoms naturally stabilize over time, even without active medications. Thus, research on the utility of pharmacotherapy early in the onset of the disorder is inconclusive.

Psychosocial Intervention to Prevent or Delay the Onset of BD

Arguably, the treatment of a child at risk for BD should begin with psychotherapy, and only progress to pharmacotherapy if the child continues to be unstable or worsens. Although requiring more time and effort than psychopharmacology, psychotherapy can be a precise, targeted intervention with sustained effects even after it is completed (Vittengl, Clark, Dunn, & Jarrett, 2007). Psychotherapy generally does not induce potentially harmful side effects. In contrast, medications such as the atypical antipsychotic olanzapine (which is frequently used as a mood stabilizer), while reducing rates of conversion to psychosis among at-risk teens, can be associated with substantial weight gain and the “metabolic syndrome” (McGlashan et al., 2006).

Medications will probably have little effect on the intensity of external stressors, and will not buffer the at-risk person against stress once he or she has discontinued taking them. In contrast, psychosocial interventions have the potential to reduce the severity of psychosocial vulnerability factors and increase the at-risk person's resiliency and coping skills when faced with adversity. When involving the family in treatment, one can also assist the caregiving parent to recognize how his or her own vulnerabilities – such as an individual history of mood disorder - translate into aversive parent/offspring interactions that may contribute to the offspring's liability to episodes.

Family-Focused Therapy

Family-focused therapy (FFT) for adult and childhood bipolar disorder begins with the assumption that negativity in the family environment, although often a product of the stress and burden of caring for an ill relative, is a risk factor for subsequent episodes of bipolar illness. FFT has three objectives: (1) to increase the family's ability to recognize the escalation of early subsyndromal symptoms, (2) to decrease family interactions characterized by high EE (criticism and hostility); and (3) to enhance the at-risk person's ability to cope with stress and adversity. This is done through three treatment modules: (1) psychoeducation for the child and family about the nature, causes, course, treatment, and self-management of bipolar illness; (2) communication enhancement training to reduce aversive communication and maximize the protective influences of the family environment; and (3) problem-solving skills to more directly reduce the impact of specific family conflicts. The application of FFT to high-risk individuals is described below.

FFT has been tested in several randomized controlled trials of adult bipolar patients. When combined with standard pharmacotherapy and compared to treatment-as-usual, FFT delays mood disorder recurrences (Miklowitz, George, Richards, Simoneau, & Suddath, 2003; Rea et al., 2003), hastens recovery from bipolar depressive episodes, elongates periods of stability, and enhances functioning following an episode (Miklowitz, Otto, Frank, Reilly-Harrington, Kogan et al., 2007; Miklowitz, Otto, Frank, Reilly-Harrington, Wisniewski et al., 2007). FFT and medication also enhanced family communication and decreased instances of medication nonadherence relative to brief psychoeducation and medication in one study (Miklowitz et al., 2003).

FFT has been examined in two open trials involving bipolar teens (Miklowitz et al., 2006; Pavuluri et al., 2004), both of which showed that combining FFT with medications led to stabilization of mania and depressive symptoms and parent-rated behavior problems. A randomized trial of FFT and medication versus brief psychoeducation and medication is currently underway (Miklowitz et al., 2006).

FFT for High-Risk Children (FFT-HR)

How would FFT be adapted to the developmental requirements of high-risk children, given that they have not yet developed bipolar illness? In the following sections, we outline the structure and content of a version of FFT for high-risk youth (FFT-HR). FFT-HR consists of 12 sessions over 4 months (8 weekly and then 4 biweekly; see Table 1). This treatment, which is carried out with the high-risk child, his or her parents, and siblings is currently being evaluated in a treatment development study by the University of Colorado, Boulder and the Stanford University School of Medicine (D. Miklowitz [PI] and K. Chang [Co-PI]; NIMH grant R34-MH077856). Consistent with the literature reviewed above, children are chosen for the study if they (a) have at least one first-degree relative with bipolar I or II disorder, (b) have a diagnosis of BD NOS, cyclothymic disorder, or major depressive disorder, and (c) currently have active symptoms of mania or depression. If the diagnosis is major depressive disorder, the child must have had active manic symptoms within the past 6 months.

The objectives of FFT-HR are to assist families to (1) recognize the symptoms of recurrent mood disorder, notably the prodromal symptoms of developing episodes, (2) understand the child's potential vulnerability to future significant mood episodes or variability; (3) accept the potential role of medications in managing mood states (where applicable), (4) distinguish mood-dysregulated behavior from normative child or teen behavior, (5) identify stress triggers for mood swings and develop plans to arrest mood escalations or deteriorations, and (6) operate at a more effective level in family communication and problem-solving.

Psychoeducation (sessions 1–4)—Families are first acquainted with the goals and expectations of the FFT program. The family is given a self-care manual (Miklowitz & George, 2007) that outlines the major symptoms of mood disorder in children, the risk factors, the most effective treatments, and self-management tools. The goal of session 2 is to acquaint the family with the signs and symptoms of severe mood disorder and its subsyndromal and prodromal forms. This task is aided by a handout that distinguishes, in three columns, "mood disorder symptoms," "mood dysregulation symptoms" and "ordinary moodiness." The handout structures the discussion of how the at-risk child's moodiness does and does not differ from what is normative for his or her age. The child is also encouraged to chart her moods and sleep/wake rhythms on a daily basis using a mood chart (www.bpkids.org).

In session 3, the family is acquainted with the FFT vulnerability/stress model (see handout in manual). The clinician explains that "genetics is not destiny" and the trajectory the child follows will depend on his or her individual balance of risk and protective factors. The role of medications in stabilizing mood and addressing biological vulnerabilities is discussed. Clinicians then ask participants to identify stressors that are currently affecting the child: family conflicts, sibling rivalries, peer or romantic relationships, or school, neighborhood, or extended family stressors.

Next, clinicians explain the nature of risk factors (e.g., alcohol and drug usage; provocative interpersonal interactions) and protective factors (e.g., compliance with medications; regular sleep/wake cycles; effective family communication and problem-solving). Methods to decrease the occurrence of behaviors that put the child at even higher risk for adverse outcomes (e.g., substance abuse, unsafe sex, drunk driving) are discussed as appropriate. A handout gives recommendations for stress reduction strategies relevant to the home environment (e.g., maintaining a tolerant and low-key family atmosphere; using emotional self-regulation techniques).

In sessions 4–5, the family develops a plan for controlling the escalation of mood swings. The relapse drill, conducted when the child is in a stable mood, outlines strategies for medical or behavioral intervention if the child's moods start to deteriorate. Parents, index children, and siblings recall previous periods of mood instability (their own and the index child's) and identify sequences consisting of *triggers, early warning signs of mood episodes,* and *palliative measures*. With the aid of a flip chart, the clinician guides the family toward an early intervention/prevention plan, typically involving no suicide/no harm contracts, emergency psychiatric reevaluations for medication changes, reducing stress triggers at home, and stabilizing sleep/wake rhythms.

Communication enhancement training (sessions 5–8) acquaints families with four skills: expressing positive feelings, active listening, making positive requests for change, and expressing negative feelings/constructive criticism. The clinician first emphasizes the link between effective family communication and mood stability (Simoneau, Miklowitz, Richards, Saleem, & George, 1999; Snyder, Castellani, & Whisman, 2006). As each skill is introduced, the family is taken through six steps: (1) learn the components of the skill with the aid of a handout (e.g., for active listening: paraphrasing, keeping eye contact), (2) observe the clinician

modeling the skill, (3) practice the skill with each other, (4) obtain feedback from the paired partner, (5) practice the skill again with the same or a different family member, and (6) complete a between-session homework task involving practicing the skill.

Problem-solving skills training (sessions 9–12) encourages families to dialogue about difficult problem topics, break down large problems (i.e., "we don't get along") into smaller ones ("we need to use lower tones of voice"), generate and evaluate the pros and cons of various solutions, agree upon a best set of solutions, and choose one or more solutions to implement (e.g., alert each other when tones of voice become aggressive). Problem-solving focuses on enhancing functional capacity and quality of life as well as symptom control. Examples of issues covered in problem-solving include strategies to increase consistency with medications, complete school homework, resolve disagreements over housework, get along with teachers, and reduce overstimulation before bedtime. Problem-solving also involves instruction in strategies for the parents or siblings to manage their own tempers or emotions (e.g., using self-talk or relaxation techniques).

The protocol is being developed on the basis of a 12-case open trial at the two sites. Feedback from these initial cases will be used to develop a clinicians' treatment manual. Once the manual has been finalized, a small scale randomized trial (N = 40) at the University of Colorado and Stanford University will examine the efficacy of FFT-HR and regular meetings with a psychiatrist versus psychiatrist meetings alone in improving the longitudinal trajectory of mania and depression symptoms, delaying the onset of first manic or hypomanic episodes, and enhancing the family's ability to advocate for appropriate care for their child.

CONCLUSIONS AND FUTURE DIRECTIONS

This review has expressed the hopeful view that bipolar disorder can be recognized in its earliest stages and treated such that the first onset of the disorder is delayed or even prevented. Family-focused treatment is one of many possible ways that early intervention could proceed; other alternatives might include interpersonal therapy to focus on management of social problems and regulation of social and circadian rhythms, or individual or group cognitive-behavioral therapy to teach adaptive thinking and emotional self-regulation skills.

Despite important advances, relatively little is known about the actual constellation of risk and protective factors that most accurately predict the onset of bipolar disorder, or the weighting of genetic, neurobiological, social, familial, or cultural factors at different stages of development. Arguably, elucidation of these developmental trajectories is a necessary precursor to fully effective preventive interventions, especially if therapeutic targets at different developmental phases could be specified. Studies that examine the interactions of genetic, neurobiological, and environmental factors should be helpful in specifying these intervention targets.

We have long known that differences in the social environment can lead to differences in gene expression and variations in brain structure or function, and recursively, that variations in genetic vulnerability or brain function can lead to the differential selection of environments. The puzzle is how best to examine the role of environmental variables while controlling for the role of genetic factors, and the reverse. Studies of the role of the environment in sibling pairs or identical twins can help control for the role of shared environmental factors and enable examination of the role of nonshared familial or other environmental factors. To borrow an example from the literature on antisocial behavior, Caspi et al. (2004) showed that, among identical twin pairs, the twin to whom the mother expressed more emotional negativity and less warmth was at greater risk for the development of antisocial behavior than the twin to whom the mother expressed less negativity and more warmth. Similar experimental designs

could be usefully applied to sibling or twin pairs in which one has bipolar disorder, to clarify how different stressors lead to differences in gene expression and the likelihood of developing mood episodes.

Understanding these diverse developmental pathways would help us to tailor our early intervention and prevention efforts, which may mean designing interventions differently for children with different prodromal presentations. For prodromal children with the highest genetic loadings for mood disorder, early intervention with medications may have a tremendous impact on later outcomes. In contrast, youths for whom environmental-contextual factors play a central role in episode onset (for example, adolescent-onset girls with a history of sexual abuse and high current family conflict) may benefit most from interventions that focus on enhancing the protective effects of the immediate social environment, with pharmacotherapy introduced only as a rescue strategy.

Finally, the results of studies of preventive interventions may elucidate the nature of genetic, biological, social, and cultural mechanisms. Indeed, if early intervention trials show that modifying family interactions reduces the risk of earlier bipolar onsets, we will have evidence that family processes play causal rather than reactive roles in some of the developmental trajectories to bipolar disorder. In parallel, if treatment-associated changes in neurobiological risk markers (such as amygdalar volume) ameliorate the trajectory of early mood symptoms or comorbidities, we can develop hypotheses about the causal primacy of these biological risk markers. The next generation of developmental research on bipolar disorder should address these questions.

Acknowledgements

Preparation of this manuscript was supported by grants MH62555, MH073871, and MH077856 to Dr. Miklowitz, a Faculty Fellowship from the University of Colorado and a Distinguished Investigator Award from the National Alliance for Research on Schizophrenia and Depression (Dr. Miklowitz), and an NIMH K-Award (Dr. Chang).

References

Akiskal HS. Developmental pathways to bipolarity: are juvenile-onset depressions pre-bipolar? Journal of the American Academy of Child and Adolescent Psychiatry 1995;34:754–763. [PubMed: 7608049]

Alda M. Bipolar disorder: From families to genes. Canadian Journal of Psychiatry 1997;42:378–387.

Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L. Antidepressant-induced mania and cycle acceleration: a controversy revisited. American Journal of Psychiatry 1995;152:1130–1138. [PubMed: 7625459]

Biederman J, Mick E, Faraone SV, Spencer T, Wilens TE, Wozniak J. Current concepts in the validity, diagnosis and treatment of paediatric bipolar disorder. International Journal of Neuropsychopharmacology 2003;6:293–300. [PubMed: 12974996]

Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Clinical course of children and adolescents with bipolar spectrum disorders. Archives of General Psychiatry 2006;63(2):175–183. [PubMed: 16461861]

Blumberg HP, Kaufman J, Martin A, Charney DS, Krystal JH, Peterson BS. Significance of adolescent neurodevelopment for the neural circuitry of bipolar disorder. Annals of the New York Academy of Sciences 2004;1021:376–383. [PubMed: 15251913]

Caetano SC, Olvera RL, Glahn D, Fonseca M, Pliszka S, Soares JC. Fronto-limbic brain abnormalities in juvenile onset bipolar disorder. Biological Psychiatry 2005;58:525–531. [PubMed: 16018982]

Carlson GA, Jensen PS, Findling RL, Meyer RE, Calabrese J, DelBello MP, et al. Methodological issues and controversies in clinical trials with child and adolescent patients with bipolar disorder: report of a consensus conference. Journal of Child and Adolescent Psychopharmacology 2003;13:13–27. [PubMed: 12804123]

Carlson GA, Weintraub S. Childhood behavior problems and bipolar disorder--relationship or coincidence? Journal of Affective Disorders 1993;28(3):143–153. [PubMed: 8408977]

Caspi A, Moffitt TE, Morgan J, Rutter M, Taylor A, Arseneault L, Tully L, Jacobs C, Kim-Cohen J, Polo-Tomas M. Maternal expressed emotion predicts children's antisocial behavior problems: using monozygotic-twin differences to identify environmental effects on behavioral development. Development and Psychopathology 2004;40:149–161.

Chang K, Adleman NE, Dienes K, Simeonova DJ, Menon V, Reiss A. Anomalous prefrontal-subcortical activation in familial pediatric bipolar disorder: a functional magnetic resonance imaging investigation. Archives of General Psychiatry 2004;61(8):781–792. [PubMed: 15289277]

Chang K, Howe M, Gallelli K, Miklowitz D. Prevention of pediatric bipolar disorder: integration of neurobiological and psychosocial processes. Annals of the New York Academy of Sciences 2006;1094:235–247. [PubMed: 17347355]

Chang K, Steiner H, Ketter T. Studies of offspring of parents with bipolar disorder. American Journal of Medical Genetics C: Seminars in Medical Genetics 2003;123:26–35.

Chang KD, Dienes K, Blasey C, Adleman N, Ketter T, Steiner H. Divalproex monotherapy in the treatment of bipolar offspring with mood and behavioral disorders and at least mild affective symptoms. Journal of Clinical Psychiatry 2003;64(936–942)

Chang KD, Steiner H, Ketter TA. Psychiatric phenomenology of child and adolescent bipolar offspring. Journal of the American Academy of Child and Adolescent Psychiatry 2000;39:453–460. [PubMed: 10761347]

Cicchetti D, Rogosch FA. Psychopathology as risk for adolescent substance use disorders: a developmental psychopathology perspective. Journal of Clinical Child Psychology 1999;28:355–365. [PubMed: 10446685]

Cicchetti D, Toth SL. The development of depression in children and adolescents. American Psychologist 1998;53(2):221–241. [PubMed: 9491749]

Correll CU, Penzner JB, Frederickson AM, Richter JJ, Auther AM, Smith CW, et al. Differentiation in the preonset phases of schizophrenia and mood disorders: evidence in support of a bipolar mania prodrome. Schizophrenia Bulletin 2007;33(3):703–713. [PubMed: 17478437]

Correll, CU.; Penzner, JB.; Kafantaris, V.; Nakayama, E.; Auther, A.; Lencz, T., et al. A lengthy and symptomatic prodrome precedes the first manic episode in early-onset bipolar disorder. Paper presented at the NIMH Pediatric Bipolar Disorders Conference; Chicago, IL. March 30; 2006.

Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL. The enduring psychosocial consequences of mania and depression. American Journal of Psychiatry 1993;150:720–727. [PubMed: 8480816]

Coville AL, Miklowitz DJ, Taylor DO, Low K. Correlates of high expressed emotion attitudes among parents of bipolar adolescents. under review

DelBello MP. The neurophysiology of childhood and adolescent bipolar disorder. CNS Spectrums 2006;11(4):298–311. [PubMed: 16641835]

DelBello MP, Adler CM, Whitsel RM, Stanford KE, Strakowski SM. A 12-week single-blind trial of quetiapine for the treatment of mood symptoms in adolescents at high risk for developing bipolar I disorder. Journal of Clinical Psychiatry 2007;68(5):789–795. [PubMed: 17503991]

Dienes KA, Hammen C, Henry RM, Cohen AN, Daley SE. The stress sensitization hypothesis: understanding the course of bipolar disorder. Journal of Affective Disorders 2006;95:43–49. [PubMed: 16837055]

Egeland JA, Blumenthal RL, Nee J, Sharpe L, Endicott J. Reliability and relationship of various ages of onset criteria for major affective disorder. Journal of Affective Disorders 1987;12(2):159–165. [PubMed: 2955008]

Egeland JA, Hostetter AM, Pauls DL, Sussex JN. Prodromal symptoms before onset of manic-depressive disorder suggested by first hospital admission histories. Journal of the American Academy of Child and Adolescent Psychiatry 2000;39(10):1245–1252. [PubMed: 11026178]

Egeland JA, Shaw JA, Endicott J, Pauls DL, Allen CR, Hostetter AM, et al. Prospective study of prodromal features for bipolarity in well Amish children. Journal of the American Academy of Child and Adolescent Psychiatry 2003;42(7):786–796. [PubMed: 12819438]

Emiroglu N, Ozerdem A, Miklowitz DJ, Baykara A, Akay A. Mood and disruptive behavior disorders and symptoms in the offspring of patients with bipolar I disorder. Journal of World Psychiatry. in press

Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? Journal of the American Academy of Child & Adolescent Psychiatry 1997;36:1378–1387. [PubMed: 9334551]

Fergus EL, Miller RB, Luckenbaugh DA, et al. Is there progression from irritability/dyscontrol to major depressive and manic symptoms? A retrospective community survey of parents of bipolar children. Journal of Affective Disorders 2003;77:71–78. [PubMed: 14550937]

Findling RL, Frazier TW, Youngstrom EA, McNamara NK, Stansbrey RJ, Gracious BL, et al. Double-blind, placebo-controlled trial of divalproex monotherapy in the treatment of symptomatic youth at high risk for developing bipolar disorder. Journal of Clinical Psychiatry 2005;68(5):781–788. [PubMed: 17503990]

Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Demeter CA, Bedoya D, et al. Early symptoms of mania and the role of parental risk. Bipolar Disorders 2005;7(6):623–634. [PubMed: 16403188]

Gallelli KA, Wagner CM, Karchemskiy A, Howe M, Spielman D, Reiss A, et al. N-acetylaspartate levels in bipolar offspring with and at high-risk for bipolar disorder. Bipolar Disorders 2005;7(6):589–597. [PubMed: 16403184]

Garber J. Depression in children and adolescents: linking risk research and prevention. American Journal of Preventive Medicine 2006;31(6 Suppl 1):S104–S125. [PubMed: 17175406]

Geller B, Tillman R, Craney JL, Bolhofner K. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Archives of General Psychiatry 2004;61:459–467. [PubMed: 15123490]

Geller B, Warner K, Williams M, Zimerman B. Prepubertal and young adolescent bipolarity versus ADHD: assessment and validity using the WASH-U-KSADS, CBCL and TRF. Journal of Affective Disorders 1998;51:93–100. [PubMed: 10743842]

Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL. Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. American Journal of Psychiatry 2001;158:125–127. [PubMed: 11136645]

Hashimoto K, Shimizu E, Iyo M. Critical role of brain-derived neurotrophic factor in mood disorders. Brain Research Review 2004;45(2):104–114.

Hasler G, Drevets WC, Gould TD, Gottesman II, Manji HK. Toward constructing an endophenotype strategy for bipolar disorders. Biological Psychiatry 2006;60:93–105. [PubMed: 16406007]

Hillegers MH, Reichart CG, Wals M, Verhulst FC, Ormel J, Nolen WA. Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. Bipolar Disorders 2005;7(4):344–350. [PubMed: 16026487]

Honig A, Hofman A, Rozendaal N, Dingemanns P. Psychoeducation in bipolar disorder: Effect on expressed emotion. Psychiatry Research 1997;72:17–22. [PubMed: 9355815]

Isometsa ET. Course, outcome, and suicide risk in bipolar disorder: a review. Psychiatric Fennica 1993;24:113–124.

Karchemskiy A, Garrett A, Howe M, Adleman N, Simeonova D, Reiss A, Chang K. Decreased amygdalar volume In familial subsyndromal bipolar disorder. under review

Kendler K. “A gene for…”: the nature of gene action in psychiatric disorders. American Journal of Psychiatry 2005;162(7):1243–1252. [PubMed: 15994704]

Kochman FJ, Hantouche EG, Ferrari P, Lancrenon S, Bayart D, Akiskal HS. Cyclothymic temperament as a prospective predictor of bipolarity and suicidality in children and adolescents with major depressive disorder. Journal of Affective Disorders 2005;85(1–2):181–189. [PubMed: 15780688]

LaPalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: a meta-analysis of risk for mental disorders. Canadian Journal of Psychiatry 1997;42:623–631.

Leibenluft E, Cohen P, Gorrindo T, Brook JS, Pine DS. Chronic vs. episodic irritability in youth: A community-based, longitudinal study of clinical and diagnostic associations. Journal of Child and Adolescent Psychopharmacology 2006;16(4):456–466. [PubMed: 16958570]

Leverich GS, McElroy SL, Suppes T, Keck PEJ, Denicoff KD, Nolen WA, et al. Early physical and sexual abuse associated with an adverse course of bipolar illness. Biological Psychiatry 2002;51:288–297. [PubMed: 11958779]

Leverich GS, Post RM, Keck PEJ, Altshuler LL, Frye MA, Kupka RW, et al. The poor prognosis of childhood-onset bipolar disorder. Journal of Pediatrics 2007;150(5):485–490. [PubMed: 17452221]

Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. Bipolar Disorders 2000;2:281–293. [PubMed: 11249806]

Lewinsohn PM, Seeley JR, Klein DN. Bipolar disorders during adolescence. Acta Psychiatrica Scandinavaca 2003;418(suppl):47–50.

Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-Depressive Association (NDMDA) survey of bipolar members. Journal of Affective Disorders 1994;31:281–294. [PubMed: 7989643]

Manji HK, Duman RS. Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. Psychopharmacology Bulletin 2001;35(2): 5–49. [PubMed: 12397885]

Masi G, Perugi G, Toni C, Millepiedi S, Mucci M, Bertini N, et al. Obsessive-compulsive bipolar comorbidity: focus on children and adolescents. Journal of Affective Disorders 2004;78:175–183. [PubMed: 15013241]

Mathews CA, Reus VI. Genetic linkage in bipolar disorder. CNS Spectrums 2003;8:891–904. [PubMed: 14978466]

McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. American Journal of Psychiatry 2006;163(5):790–799. [PubMed: 16648318]

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Archives of General Psychiatry 2007;64(5):543–552. [PubMed: 17485606]

Meyer SE, Carlson GA, Wiggs EA, Ronsaville DS, Martinez PE, Klimes-Dougan B, et al. A prospective high-risk study of the association among maternal negativity, apparent frontal lobe dysfunction, and the development of bipolar disorder. Development and Psychopathology 2006;18(2):573–589. [PubMed: 16600068]

Miklowitz DJ, Biuckians A, Richards JA. Early-onset bipolar disorder: a family treatment perspective. Development and Psychopathology 2006;18(4):1247–1265. [PubMed: 17064437]

Miklowitz, DJ.; George, EL. The bipolar teen: what you can do to help your teen and your family. New York: Guilford Publications; 2007.

Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Archives of General Psychiatry 2003;60:904–912. [PubMed: 12963672]

Miklowitz DJ, Goldstein MJ, Nuechterlein KH, Snyder KS, Mintz J. Family factors and the course of bipolar affective disorder. Archives of General Psychiatry 1988;45:225–231. [PubMed: 3341878]

Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Kogan JN, Sachs GS, et al. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: results from a 9-month randomized controlled trial. American Journal of Psychiatry 2007;164(9):1–8. [PubMed: 17202533]

Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Wisniewski SR, Kogan JN, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. Archives of General Psychiatry 2007;64:419–427. [PubMed: 17404119]

Miklowitz DJ, Simoneau TL, George EL, Richards JA, Kalbag A, Sachs-Ericsson N, Suddath R. Family-focused treatment of bipolar disorder: One-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biological Psychiatry 2000;48:582–592. [PubMed: 11018229]

Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Archives of General Psychiatry 2007;64(9):1032–1039. [PubMed: 17768268]

Murray L, Kempton C, Woolgar M, Hooper R. Depressed mothers' speech to their infants and its relation to infant gender and cognitive development. Journal of Child Psychology and Psychiatry 1993;34 (7):1083–1101. [PubMed: 8245134]

NIMH. Research roundtable on prepubertal bipolar disorder. Journal of the American Academy of Child and Adolescent Psychiatry 2001;40:871–878. [PubMed: 11501685]

O'Connell RA, Mayo JA, Flatow L, Cuthbertson B, O'Brien BE. Outcome of bipolar disorder on long-term treatment with lithium. British Journal of Psychiatry 1991;159:132–129.

Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. Journal of the American Academy of Child & Adolescent Psychiatry 2005;44(9):846–871. [PubMed: 16113615]

Pavuluri MN, Graczyk PA, Henry DB, Carbray JA, Heidenreich J, Miklowitz DJ. Child and family-focused cognitive behavioral therapy for pediatric bipolar disorder: development and preliminary results. Journal of the American Academy of Child & Adolescent Psychiatry 2004;43:528–537. [PubMed: 15100559]

Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biological Psychiatry 2004;55:875–881. [PubMed: 15110730]

Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biological Psychiatry 2003;54:515–528. [PubMed: 12946880]

Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. American Journal of Psychiatry 1992;149:999–1010. [PubMed: 1353322]

Post RM. Do the epilepsies, pain syndromes, and affective disorders share common kindling-like mechanisms? Epilepsy Research 2002;50(1–2):203–219. [PubMed: 12151130]

Post RM, Leverich GS. The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: The need for earlier and alternative modes of therapeutic intervention. Development and Psychopathology 2006;18(4):1181–1211. [PubMed: 17064434]

Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. Biological Psychiatry 2000;48(8):766–777. [PubMed: 11063973]

Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. Biological Psychiatry 2001;49(9):741–752. [PubMed: 11331082]

Rea MM, Tompson M, Miklowitz DJ, Goldstein MJ, Hwang S, Mintz J. Family focused treatment vs. individual treatment for bipolar disorder: results of a randomized clinical trial. Journal of Consulting and Clinical Psychology 2003;71:482–492. [PubMed: 12795572]

Reichart CG, Nolen WA. Earlier onset of bipolar disorder in children by antidepressants or stimulants? An hypothesis. Journal of Affective Disorders 2004;78(1):81–84. [PubMed: 14672801]

Rich BA, Vinton DT, Roberson-Nay R, Hommer RE, Berghorst LH, McClure EB, et al. Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. Proceedings of the National Academy of Sciences 2006;103(23):8900–8905.

Shaw JA, Egeland JA, Endicott J, Allen CR, Hostetter AM. A 10-year prospective study of prodromal patterns for bipolar disorder among Amish youth. Journal of the American Academy of Child and Adolescent Psychiatry 2005;44(11):1104–1011. [PubMed: 16239857]

Simoneau TL, Miklowitz DJ, Richards JA, Saleem R, George EL. Bipolar disorder and family communication: Effects of a psychoeducational treatment program. Journal of Abnormal Psychology 1999;108:588–597. [PubMed: 10609423]

Singh MK, DelBello MP, Kowatch RA, Strakowski SM. Co-occurrence of bipolar and attention-deficit hyperactivity disorders in children. Bipolar Disorders 2006;8(6):710–720. [PubMed: 17156157]

Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. American Journal of Medical Genetics, Part C: Seminars in Medical Genetics 2003;123(1):48–58.

Snyder DK, Castellani AM, Whisman MA. Current status and future directions in couple therapy. Annual Review of Psychology 2006;57:1–28.

Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Molecular Psychiatry 2005;10(1):105–116. [PubMed: 15340357]

Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, et al. Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. American Journal of Psychiatry 2002;159:1841–1847. [PubMed: 12411217]

Suppes T, Leverich GS, Keck PE, Nolen WA, Denicoff KD, Altshuler LL, et al. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. Journal of Affective Disorders 2001;67:45–59. [PubMed: 11869752]

Tillman R, Geller B. Controlled study of switching from attention-deficit/hyperactivity disorder to a prepubertal and early adolescent bipolar I disorder phenotype during 6-year prospective follow-up: rate, risk, and predictors. Development and Psychopathology 2006;18(4):1037–1053. [PubMed: 17064428]

Tillman R, Geller B, Nickelsburg MJ, Bolhofner K, Craney JL, DelBello MP, et al. Life events in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. Journal of Child and Adolescent Psychopharmacology 2003;13(3): 243–251. [PubMed: 14661614]

Verhulst FC, van der Ende J, Ferdinand RF, Kasius MC. The prevalence of DSM-III-R diagnoses in a national sample of Dutch adolescents. Archives of General Psychiatry 1997;54(4):329–336. [PubMed: 9107149]

Vittengl JR, Clark LA, Dunn TW, Jarrett RB. Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-behavioral therapy's effects. Journal of Consulting and Clinical Psychology 2007;75(3):475–488. [PubMed: 17563164]

Wals M, Hillegers MHJ, Reichart CG, Verhulst FC, Nolen WA, Ormel J. Stressful life events and onset of mood disorders in children of bipolar parents during 14-month follow-up. Journal of Affective Disorders 2005;87:253–263. [PubMed: 15979149]

Yan LJ, Hammen C, Cohen AN, Daley SE, Henry RM. Expressed emotion versus relationship quality variables in the prediction of recurrence in bipolar patients. Journal of Affective Disorders 2004;83:199–206. [PubMed: 15555714]

Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disorders 2000;2(3 Pt 2):237–248. [PubMed: 11249801]

Table 1

Session by Session Plan for the Family-Focused treatment for High Risk Youth (FFT-HR)

Session number	Goals
1	Preview FFT-HR Acquaint family with goals, format and expectations Begin to develop treatment alliance
2	Acquaint family with symptoms and signs of bipolar disorder as well as its prodromal forms Create individualized self-rated mood chart Address child and family's questions, doubts, and concerns
3	Introduce the vulnerability/stress model Construct a list of family and individual stressors
4	Identify risk and protective factors Prevention planning
5	Preview skills of communication training Expressing positive feelings
6	Skill #2: Active listening
7	Skill #3: Making positive requests for change
8	Skill #4: Expressing negative feelings
9–11	Introduce the module problem solving Identify specific problems for problem solving Complete problem solving steps
12	Termination Review treatment objectives and prevention plans Encourage treatment adherence Make referrals for ongoing and future care