Bipolar Offspring: A Window into Bipolar Disorder Evolution

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Children of parents with bipolar disorder (bipolar offspring) represent a rich cohort for study with potential for illumination of prodromal forms of bipolar disorder. Due to their high-risk nature, bipolar offspring may present phenomenological, temperamental, and biological clues to early presentations of bipolar disorder. This article reviews the evidence for establishing bipolar offspring as a high-risk cohort, the studies which point to possible prodromal states in bipolar offspring, biological findings in bipolar offspring which may be indicators of even higher risk for bipolar disorder, initial attempts at early intervention in prodromal pediatric bipolar disorder, and implications for future research. Biol Psychiatry 2003; 53:945–951 © *2003 Society of Biological Psychiatry*

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Introduction

Children of parents with bipolar disorder (BD) (heretofore referred to as "bipolar offspring") represent a rich cohort for study with potential for illumination of prodromal forms of BD. It has been well established that bipolar offspring are at high risk for development of BD (DelBello and Geller 2001). Due to their high-risk nature, bipolar offspring may present phenomenological, temperamental, and biological clues to early presentations of BD. Bipolar offspring are also genetically less diverse than bipolar samples that are mixed for presence or absence of family history. Bipolar offspring who have not yet developed BD or other serious psychiatric illness also may be a relatively "pure" population to study. They often have not had exposure to psychotropic medications or years of substance abuse, both of which can confound determination of cause or effect in both phenomenological and biological presentation.

Granted, bipolar offspring often have had exposure to significant environmental stressors, such as having a parent with bipolar disorder who may be prone to mood episodes, substance abuse, and hospitalizations (Chang et al 2001). As quantifying the contribution of environmental factors to development of psychopathology is difficult, assessment of bipolar offspring at as young an age as possible is important. Yet, not all bipolar offspring will develop BD (indeed, the majority will not). In the absence of firm indications of the central pathogenic processes involved in BD, it would be difficult to predict from an early age which particular offspring will develop BD. Thus, it may be more efficient to concentrate on those offspring with early psychiatric difficulties; however, the natural evolution of early syndromes in at-risk offspring has not been established. Some may not progress at all to BD or may progress to an entirely different disorder.

Disruptive behavioral disorders have been postulated to be early precursors to bipolar disorder in certain children (Carlson and Weintraub 1993). While disruptive behavior disorders are themselves not uncommon in children, their presence in bipolar offspring may raise the risk of BD development above those of nonbipolar offspring; however, it is unlikely that the presence of these disorders alone in offspring would be good indicators of impending BD. More likely, as will be discussed, a combination of mood difficulties and disruptive behavior disorders is a more specific marker of prodromal BD. If such children were indeed prodromal for fully developed BD, then study of these children would be crucial for identification of prodromal states, leading to the possibility of early intervention and prevention of worsening symptoms and poorer outcome. This article will review the evidence for establishing bipolar offspring as a high-risk cohort, the studies which point to possible prodromal states in bipolar offspring, biological findings in bipolar offspring which may be indicators of even higher risk for BD, initial attempts at early intervention in prodromal pediatric BD, and implications for future research.

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The Epidemiologic/Phenomenological Argument

Children of bipolar parents have been well established to be at higher risk than the general population or control samples for development of BD. A meta-analysis of studies conducted before 1997 found bipolar offspring to be 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 et al 1997). Since 1997, cross-sectional studies have continued to report that approximately 50% of bipolar offspring meet criteria for at least one DSM-IV psychiatric disorder (Chang et al 2000; Duffy et al 1998; Soutullo, unpublished data). In these studies, the incidence of bipolar spectrum disorders (including bipolar I, II, and cyclothymia) has mostly ranged from 14% to 50%. The one exception is a study from the Netherlands of a Dutch cohort, which found BD in only 4 out of 140 (2.8%) bipolar offspring (Wals et al 2001). The authors proposed a transatlantic explanation, citing much less use of antidepressants and stimulants in European countries compared to the United States, which might lead to fewer cases of BD caused by pharmacologically induced mania; however, there was still a 27% incidence of mood disorders in these offspring, raising the possibility that offspring with prodromal BD forms were included in this category.

High incidences of attention-deficit/hyperactivity disorder (ADHD) also have been consistently reported in bipolar offspring studies since the early 1970s. Problems with conduct and general behavior were reported in bipolar offspring before the advent of DSM-III-R and operationalization of the criteria for ADHD (Davis 1979; Kestenbaum 1979). In 1983, the syndrome of ADHD was first reported in a bipolar offspring sample (Decina et al 1983). Since 1988, approximately 27% of bipolar offspring studied have been reported as meeting criteria for ADHD (Carlson and Weintraub 1993; Chang et al 2000; Duffy et al 1998; Grigoroiu-Serbanescu et al 1989; Hammen et al 1990; Radke-Yarrow et al 1992; Soutullo 2000; Zahn-Waxler et al 1988).

The reasons for this increasingly high incidence of ADHD in bipolar offspring may be multifactorial. Psychosocial and environmental changes in the United States over the last 50 years may be causing higher prevalence of ADHD symptoms, especially in girls (Robison et al 2002). Better diagnostic tools and criteria for ADHD and more availability of effective treatments may lead to increased diagnoses. Finally, an increase in ADHD diagnoses among bipolar offspring may actually reflect an increase of early-onset BD in the general population. First, ADHD is highly comorbid with pediatric BD (Faraone et al 1997b; Wozniak et al 1995a). Second, it has been postulated that the presentation of childhood ADHD with later BD development may represent a subtype of early-onset BD (Chang et al 2000; Faraone et al 1997a; Sachs et al 2000; Wozniak et al 1995b). Thus, cross-sectional evaluation of bipolar offspring that detects ADHD may be detecting early symptoms and a syndrome which could evolve into BD.

The reasons for an increase in detection of BD in bipolar offspring studies in the United States are potentially similar to those for the increase in detection of ADHD. Awareness of the possibility of bipolar spectrum disorders in youth has undoubtedly spurred greater research with a keener eye to detect BD. Semistructured diagnostic interviews such as the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al 1996) have been created to specifically elicit symptoms of early-onset BD. Increased treatment of bipolar offspring with antidepressants or psychostimulants may be contributing to earlier onset of BD (DelBello et al 2001; Soutullo et al 2002). Finally, an additional mechanism for the increased incidence of BD in bipolar offspring cohorts may be that successive generations in families with BD may be developing BD at earlier ages, leading to increased detection in child and adolescent samples. This concept of genetic anticipation in BD is discussed later in this review (Goossens et al 2001).

The high incidence of ADHD and BD detected in bipolar offspring cohorts supports this sample as a useful population for study, especially when investigating prodromal forms of BD.

Subsyndromal/Prodromal Bipolar Disorder

The realization from both retrospective (and some prospective) data that the majority of BD cases begin in childhood or adolescence has led to some study of putative prodromal forms of BD in childhood. A *prodrome* may be defined as a state in which populations at risk for development of a disorder have accumulated enough risk factors to exhibit significant early symptoms of the disorder, which if left untreated, would ordinarily lead to full expression of the disorder. Such an evolution of disease progression is analogous to the incubation period of an infectious organism before a fever begins or the gradual accumulation of atherosclerotic plaques before a myocardial infarction occurs. Thus, the model of bipolar disorder in evolution is consistent with other medical models of disease.

Subsyndromal forms of BD have been described in 6% to 13% of nonscreened adolescent populations (Carlson and Kashani 1988; Lewinsohn et al 1995). Whether these children are experiencing prodromal BD relies on future longitudinal assessment. One study did report that while 6% of a high school sample of adolescents had significant, but subsyndromal, symptoms of mania, none met criteria

for full bipolar I disorder upon follow-up in their early 20s (Lewinsohn et al 2000). This finding raises the question of what syndromes bipolar offspring studies may be capturing. That is, cross-sectional assessment of children at risk for BD may be capturing individuals in prodromal states of bipolar I disorder, bipolar II disorder, or a disorder that does not fully meet bipolar I or II criteria (i.e., a subsyndromal BD or bipolar disorder not otherwise specified). In the Lewinsohn et al (2000) follow-up study, however, children with subsyndromal BD had as much psychosocial dysfunction as subjects with bipolar I disorder, calling into question the clinical relevance of the symptom count and duration criteria required for a DSM-IV diagnosis of bipolar I disorder. Furthermore, subtypes of BD that do not have notable prodromal symptoms may be missed by assessing child bipolar offspring. For example, classic manic-depressive illness may lack prodromal psychopathology and instead present with a "first-break" manic episode (Kutcher et al 1998; Strober et al 1988). This variant, which appears less common in prepubertal and early adolescent children (Findling et al 2001; Geller et al 2002), may include euphoric and grandiose mania and later (15–19 years old) onset and may also be familial but may or may not demonstrate anticipation in successive generations. Other examples of bipolar subtypes which would be overlooked by the offspring approach include BD which only arose after events such as childbirth (postpartum onset), reflecting a subtype requiring a particular hormonal component that might not be achieved through puberty alone, or BD due to other etiologies (birth trauma, infectious) which have not been established but which may lead to isolated cases of BD without a positive family history. Yet, these phenotypes may appear similar phenomenologically to familial BD.

Despite the phenotypic heterogeneity of BD, studying cohorts of children with a parent meeting full bipolar I or II criteria may serve to preferentially identify prodromal forms of bipolar I or II disorder, most likely an early-onset variety. Our group reported on psychiatric symptoms and diagnoses in a cohort of 60 such bipolar offspring (Chang et al 2000). In addition to finding high rates of ADHD (27%), depression (15%), BD (13%), and anxiety disorders (11%), we sought to identify psychiatric symptoms and temperament characteristics possibly indicative of prodromal BD. First, we found that offspring who had bilineal pedigrees of mood disorder (BD in one parent, BD or unipolar depression in the other) had higher WASH-U-KSADS scores of irritability, depression, rejection sensitivity, and lack of mood reactivity than bipolar offspring with unilineal pedigrees (Chang et al 2000). Next, in comparing parental reports of temperament in these bipolar offspring to national means on the Dimensions of Temperament Survey-Revised (DOTS-R), we found that offspring with already syndromal BD had high levels of general activity, less ability to stay on task, and low flexibility or adaptability (Chang et al, in press b). Finally, parents with BD who themselves reported childhood ADHD were more likely to have a child with already syndromal BD than parents with BD who did not have ADHD as children. Presence of BD and ADHD in a parent may therefore be an additional risk factor for early development of BD. This theory is corroborated by a retrospective study in which adults with BD and ADHD reported earlier onset of BD than adults with only BD (Sachs et al 2000). That is, presence of ADHD in these cohorts familial for BD may indicate a subtype of BD that presents earlier in childhood and is transmittable to offspring.

Therefore, one likely characterization of prodromal BD would include psychiatric symptoms and/or diagnoses such as disruptive behavior disorders, especially ADHD, and temperamental characteristics of difficulties with mood regulation, high activity levels, and low flexibility. This characterization is somewhat similar to the temperament construct of behavioral disinhibition, which has been linked to the development of disruptive behavioral disorders (Hirshfeld-Becker et al 2002). Additional evidence of a biological parent with BD, especially one with a childhood history of ADHD, would support this *BD* in evolution diagnosis; however, as mentioned earlier, there are likely multiple specific presentations of prodromal BD, as there are multiple subtypes of the disorder. Due to the possibility of genetic anticipation in any bipolar offspring cohort, we may be identifying specifically prodromal forms of a familial early-onset (pediatric) BD.

Longitudinal phenomenological evaluation of our entire sample, which is planned, is necessary to include the complexities of varying phenotypes of bipolar disorder with varying ages of onset in this study. For example, offspring currently unaffected by psychopathology should be followed to examine the possibility of a first-episode mania in young adulthood. If these subjects never develop psychopathology, then temperament, biological, and genetic factors could be studied to determine resiliency factors, which may have prevented bipolar onset. Our subjects with putative prodromal BD need to be followed longitudinally to determine if they truly will develop fully syndromal bipolar I or II disorder or will remain subsyndromal. Finally, offspring with other disorders should be followed to establish alternate pathways prodromal to BD. Indeed, we have noted high incidences of current and past anxiety disorders in bipolar offspring, predominantly separation anxiety (Chang et al 2000). Without longitudinal follow-up, it is unclear if this anxiety stems from the chaotic home environment and attachment difficulties in these children, reflects the background "noise" from the

high prevalence of transitory anxiety disorders in children, or represents another evolutionary pathway toward BD.

The high-risk offspring approach has also been used to investigate early forms of other psychiatric disorders. For example, studies of offspring of schizophrenic parents have found an 8.5% to 20% incidence of schizophrenia and a high incidence of related disorders, such as schizoaffective disorder or Cluster A personality disorders (Erlenmeyer-Kimling 2000). Researchers have also reported early neurologic or neuromotor deficits, along with smooth-pursuit eye movement dysfunction, to be potential markers of genetic liability for schizophrenia in offspring of schizophrenic parents. A realistic goal would therefore be to identify such early manifestations or signs of evolving BD in bipolar offspring.

Biological Studies in Bipolar Offspring

Biological markers associated with BD would aid in reliably identifying prodromal forms of BD; however, no such markers have yet been established in adults or children. Technologies such as brain imaging have provided much information regarding the neurobiological condition of adults with BD, most with fairly long durations of BD. Thus, it is difficult to establish whether the findings were present before the onset of BD or if they occurred afterwards. Furthermore, many patients with BD have been exposed to years of psychotropic medications and/or illicit substances. To identify markers of risk for BD, it is necessary to study a high-risk sample, such as bipolar offspring, and perform serial longitudinal assessments covering the time needed to fully develop BD; however, it should be noted that any such biological marker discovered may reflect either a trait that predisposes toward BD or a biological change inflicted by the disorder before clinically relevant symptoms appear. In either case, early identification of such a marker could allow for intervention and prevention of the full disorder.

Neurophysiology

There have been negative findings regarding differences in epidermal conductivity (Zahn et al 1989) and eye-tracking (Rosenberg et al 1997) in bipolar offspring compared to controls; however, a study of melatonin suppression by bright light found that bipolar offspring had increased suppression of melatonin compared to healthy controls (Nurnberger et al 1988). This finding has not since been replicated or expanded, but it is nevertheless interesting given the role of melatonin in circadian rhythms and the possibility of disrupted circadian rhythms as partially etiologic in BD (Wehr et al 1983).

Neuroimaging

Neuroimaging studies may eventually prove useful for revealing neuropathophysiological risk factors for BD development due to the availability of noninvasive modalities and ability to directly study the involved end organ. Comparing studies of youth and adults with BD may also reveal insights into the evolution of neuroanatomic and neurophysiologic changes seen in adult BD. One magnetic resonance imaging (MRI) study reported increased hippocampal size in bipolar offspring with mixed psychiatric presentations, ranging from symptom-free to mood disordered, but none having syndromal BD (DelBello et al, unpublished data). Using magnetic resonance spectroscopy (MRS), our group found that whereas bipolar offspring with BD had decreased N-acetyl-aspartate (NAA) to creatine (Cr) ratios in the right dorsolateral prefrontal cortex (DLPFC) (Chang et al, in press a), bipolar offspring with mood and disruptive behavioral disorders, but not BD, had unchanged DLPFC NAA/Cr ratios (Chang et al, unpublished data). This preliminary study suggests that NAA would therefore not be a suitable marker for prodromal BD, as levels may not begin to decrease until either after development of BD or, as most of the offspring studied were taking medication, after significant psychotropic medication exposure. This possibility is supported by a tendency of NAA/Cr ratios to decrease as illness duration increased (Chang et al, in press a). Furthermore, decreased prefrontal NAA also has been reported in schizophrenia (Bertolino et al 1998) and ADHD (Hesslinger et al 2001), making it nonspecific for BD.

Other candidate brain areas for study may be derived from the literature regarding neuroimaging of adult bipolar cohorts. Decreased subgenual prefrontal gray matter, glia, and blood flow have been reported in adults with BD with strong family histories of BD (Drevets et al 1997; Ongur et al 1998). Decreased cerebellar volume, including decreased vermal size, also has been described in adult patients with familial, but not nonfamilial, BD (Brambilla et al 2001). Patients with familial BD also may have left lateral ventricular enlargement compared to controls (Brambilla et al 2001). Therefore, specific brain regions may be structurally or functionally abnormal in familial BD and should be investigated in bipolar offspring to establish whether these findings are present before the onset of BD. Other volumetric, MRS, and functional MRI studies need to be performed on cohorts of bipolar offspring to further identify preexisting neurobiological characteristics of prodromal BD.

Genetics

The ultimate biological marker would be a genetic one, as identification of a genetic method for quantifying bipolar

predisposition could lead to very early intervention. While the search for reliable genetic markers of BD continue, few researchers have concentrated on at-risk cohorts. As mentioned earlier, a mechanism which may be involved in lineages with heavy loading for BD is genetic anticipation. *Anticipation*, defined as greater severity and/or earlier age at onset (AAO) of the disorder in subsequent generations, has been described in numerous familial cohorts (Goossens et al 2001; McInnis et al 1993); however, these studies predominantly have relied on retrospective reporting of AAO. The intrinsic problems of relying on memory to quantify AAO and severity of BD argue for prospective studies of at-risk cohorts. Thus, one such study would follow at-risk offspring through the age of high likelihood for development of BD and then follow their biological children as well. This type of study may be prohibitive temporally; searching for genetic, rather than familial, markers would expedite this research. The available evidence suggests that unstable trinucleotide repeats (e.g., CAG), which are transmitted in greater lengths to successive generations, may be the biological basis of the clinical phenomenon of genetic anticipation (Goossens et al 2001). Study of these repeats and other linkage studies in cohorts of parents with BD and their offspring would generate valuable information regarding potential. That is, affected parents and affected offspring could be studied, along with unaffected or prodromal offspring or siblings. Establishment of gradations of illness with amount of repeat expansion, for example, could lead to discovery of the role of repeat expansion in BD development, such as disruption of transcription of a nearby gene; however, as of yet, the presence of anticipation in cohorts with BD has not been successfully linked to any specific trinucleotide repeat sequence or gene.

Additionally, there are ethical issues when discussing the possibility of identifying disease risk factors in utero, namely involving elective abortion. These issues are beyond the scope of this review but should be mentioned in any discussion of genetic testing.

Early Intervention Studies

The identification of prodromal BD in children and adolescents would mean the possibility of early intervention and prevention of the full expression of BD in these children. To develop intervention strategies for bipolar offspring, it is helpful to use a model for BD development. One elegant model of the development and progression of BD is the kindling model as applied to mood disorders, as proposed by Post (1992). In this model, psychosocial stressors interact with genetic predisposition predominantly at the outset of the disorder. These stressors may effect neurobiological change that not only leads to affective episodes but may also create vulnerability to future episodes. Thus, prevention of this trajectory would involve either increasing the neurobiological buffer to withstand these stressors (by pharmacology or psychotherapy) or by actually decreasing the amount or intensity of the stressors. From a psychosocial standpoint, early intervention could therefore consist of family therapies to improve dysfunctional family interactions, psychoeducation to parents regarding parenting skills and early signs of BD to monitor, or direct psychotherapy with the at-risk child to increase his or her ability to cognitively and emotionally handle stress. These interventions also may not carry as much concern as using pharmacologic agents that have uncertain effects on developing central nervous systems; however, these psychosocial interventions may be difficult to implement and their efficacy in preventing BD development may be difficult to study without adequate control arms.

The second approach involves pharmacology. Appropriate medications would first treat subsyndromal symptoms, such as mood or ADHD symptoms, adequately without furthering the progression to BD. For example, antidepressants may be relatively poor choices to treat depression or anxiety symptoms in bipolar offspring due to the risk of directly causing a manic episode (Chang and Ketter 2001). Second, proposed medications should be able to halt, or even reverse, the neurobiological progression toward BD as hypothesized by the kindling model. There are some early data suggesting that lithium and certain anticonvulsants may have neuroprotective qualities (Manji and Chen 2002; Manji et al 2000; Young et al 2002). Therefore, these agents, which are already being used to treat BD, may be good candidates for study in bipolar offspring cohorts. We and other groups have begun such early intervention trials using these mood stabilizers. In our first efforts of intervention, 79% of 24 bipolar offspring with mood and/or disruptive behavioral disorders (major depressive disorder, ADHD, cyclothymia), but not bipolar I or II disorder, improved after 12 weeks of open divalproex monotherapy (Chang et al, in press c). Response was considered a "1" or a "2" ("marked" or "moderate improvement") on the Clinician Global Impression-Improvement scale. Secondary response criteria were a 50% decrease on either the Young Mania Rating Scale or the 28-item Hamilton Depression Rating Scale. Improvements were seen primarily in depressive and manic symptoms and general functioning; however, while this intervention may have prophylactic effects as well, the efficacy of divalproex in preventing the onset of fully developed BD cannot be determined until longitudinal monitoring and comparison to a control group (e.g., bipolar offspring with putative prodromal BD who are not medicated) are done.

A similar study of bipolar offspring with either cyclothymia or bipolar disorder not otherwise specified (NOS) is currently in progress. The researchers in this study

anticipate enrollment of 60 children and adolescents in this 8-week prospective, randomized, placebo-controlled study (Findling et al 2000). This type of placebo-controlled trial is essential for studying the acute efficacy of antikindling agents in offspring with subsyndromal BD. Comparison studies of mood stabilizers in nonbipolar offspring cohorts with similar symptomatology would help establish the specificity of using response to mood stabilizer treatment as a probe for impending BD development. Delineation of subjects who responded well might indicate those subjects who are truly evolving toward bipolar development.

Caution should be exercised, however, in implementing pharmacologic early intervention in symptomatic bipolar offspring at this point. Some prodromes may be self-limiting and not progress to BD, and effects of certain medications on the developing brain are still not well understood (Gottesman and Erlenmeyer-Kimling 2001).

Discussion

American medicine, for many complex reasons, has emphasized illness treatment more so than prevention. Most private and federal funding in bipolar disorder has concentrated on discovery of treatments, not methods of prophylaxis, for BD. Attenuation or prevention of BD has the potential to yield massive social and financial savings. Study of bipolar offspring represents one unique opportunity to the further understanding of early prodromal forms of BD, which ultimately may lead to early identification and attenuation or prevention of the full disorder. Thus, the study of bipolar offspring is important for at least three reasons:

- Theoretical: BD is a disorder with a known genetic substrate that has a specific period of onset and often an extended prodromal period during which the gene-environment interaction can be examined.
- Clinical: Early intervention may lead to prevention of progression of BD and create the possibility of finding curative agents, a rarity in psychiatry.
- Public Health: BD carries great socioeconomic impact (Begley et al 2001), and the cost savings of preventative intervention to society can be demonstrated.

Further studies of bipolar offspring cohorts need to be performed longitudinally and include careful psychiatric assessment and inclusion of meaningful probes for neurobiological abnormalities which may ultimately provide signals for evolving bipolar disorder.

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References

Begley CE, Annegers JF, Swann AC, Lewis C, Coan S, Schnapp WB, et al (2001): The lifetime cost of bipolar disorder in the US: An estimate for new cases in 1998. *Pharmacoeconomics* 19:483–495.

Bertolino A, Callicott JH, Nawroz S, Mattay VS, Duyn JH, Tedeschi G, et al (1998): Reproducibility of proton magnetic resonance spectroscopic imaging in patients with schizophrenia. *Neuropsychopharmacology* 18:1–9.

Brambilla P, Harenski K, Nicoletti M, Mallinger AG, Frank E, Kupfer DJ, et al (2001): MRI study of posterior fossa structures and brain ventricles in bipolar patients. *J Psychiatr Res* 35:313–322.

Carlson GA, Kashani JH (1988): Manic symptoms in a non-referred adolescent population. *J Affect Disord* 15:219–226.

Carlson GA, Weintraub S (1993): Childhood behavior problems and bipolar disorder–relationship or coincidence? *J Affect Disord* 28:143–153.

Chang KD, Adleman N, Dienes K, Reiss A, Ketter TA (in press a): Decreased n-acetylaspartate in children with familial bipolar disorder. *Biol Psychiatry*.

Chang KD, Blasey C, Ketter TA, Steiner H (2001): Family environment of children and adolescents with bipolar parents. *Bipolar Disord* 2:68–72.

Chang KD, Blasey C, Ketter TA, Steiner H (in press b): Temperament characteristics of bipolar offspring. *J Affect Disord.*

Chang KD, Dienes K, Blasey C, Adleman NE, Steiner H, Ketter TA (in press c): Divalproex in the treatment of bipolar offspring with mood and behavioral disorders and at least mild affective symptoms. *J Clin Psychiatry.*

Chang KD, Ketter TA (2001): Special issues in the treatment of paediatric bipolar disorder. *Expert Opin Pharmacother* 2:613–622.

Chang KD, Steiner H, Ketter TA (2000): Psychiatric phenomenology of child and adolescent bipolar offspring. *J Am Acad Child Adolesc Psychiatry* 39:453–460.

Davis RE (1979): Manic-depressive variant syndrome of childhood: A preliminary report. *Am J Psychiatry* 136:702–706.

Decina P, Kestenbaum CJ, Farber S, Kron L, Gargan M, Sackeim HA, et al (1983): Clinical and psychological assessment of children of bipolar probands. *Am J Psychiatry* 140:548–553.

DelBello MP, Geller B (2001): Review of studies of child and adolescent offspring of bipolar parents. *Bipolar Disord* 3:325–334.

DelBello MP, Soutullo CA, Hendricks W, Niemeier RT, McElroy SL, Strakowski SM (2001): Prior stimulant treatment in adolescents with bipolar disorder: Association with age at onset. *Bipolar Disord* 3:53–57.

Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, et al (1997): Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386:824–827.

Duffy A, Alda M, Kutcher S, Fusee C, Grof P (1998): Psychiatric symptoms and syndromes among adolescent children of parents with lithium-responsive or lithium-nonresponsive bipolar disorder. *Am J Psychiatry* 155:431–433.

Erlenmeyer-Kimling L (2000): Neurobehavioral deficits in offspring of schizophrenic parents: Liability indicators and predictors of illness. *Am J Med Genet* 97:65–71.

Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T (1997a): Attention-deficit hyperactivity disorder with bipolar disorder: A familial subtype? *J Am Acad Child Adolesc Psychiatry* 36:1378–1390.

Faraone SV, Biederman J, Wozniak J, Mundy E, Mennin D, O'Donnell D (1997b): Is comorbidity with ADHD a marker for juvenile-onset mania? *J Am Acad Child Adolesc Psychiatry* 36:1046–1055.

Findling RL, Gracious BL, McNamara NK, Calabrese JR (2000): The rationale, design, and progress of two novel maintenance treatment studies in pediatric bipolarity. *Acta Neuropsychiatrica* 12:136–138.

Findling RL, Gracious BL, McNamara NK, Youngstrom EA, Demeter CA, Branicky LA, et al (2001): Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. *Bipolar Disord* 3:202–210.

Geller B, Zimerman B, Williams M, Delbello MP, Frazier J, Beringer L (2002): Phenomenology of prepubertal and early adolescent bipolar disorder: Examples of elated mood, grandiose behaviors, decreased need for sleep, racing thoughts and hypersexuality. *J Child Adolesc Psychopharmacol* 12:3–9.

Geller BG, Williams M, Zimerman B, Frazier J (1996): *WASH-U-KSADS (Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia)*. St. Louis, Missouri: Washington University.

Goossens D, Del-Favero J, Van Broeckhoven C (2001): Trinucleotide repeat expansions: Do they contribute to bipolar disorder? *Brain Res Bull* 56:243–257.

Gottesman II, Erlenmeyer-Kimling L (2001): Family and twin strategies as a head start in defining prodromes and endophenotypes for hypothetical early-interventions in schizophrenia. Schizophr Res 51:93–102.

Grigoroiu-Serbanescu M, Christodorescu D, Jipescu I, Totoescu A, Marinescu E, Ardelean V (1989): Psychopathology in children aged 10–17 of bipolar parents: Psychopathology rate and correlates of the severity of the psychopathology. *J Affect Disord* 16:167–179.

Hammen C, Burge D, Burney E, Adrian C (1990): Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder. *Arch Gen Psychiatry* 47:1112–1117.

Hesslinger B, Thiel T, Tebartz van Elst L, Hennig J, Ebert D (2001): Attention-deficit disorder in adults with or without hyperactivity: Where is the difference? A study in humans using short echo (1)H- magnetic resonance spectroscopy. *Neurosci Lett* 304:117–119.

Hirshfeld-Becker DR, Biederman J, Faraone SV, Violette H, Wrightsman J, Rosenbaum JF (2002): Temperamental correlates of disruptive behavior disorders in young children: Preliminary findings. *Biol Psychiatry* 51:563–574.

Kestenbaum CJ (1979): Children at risk for manic-depressive illness: Possible predictors. *Am J Psychiatry* 136:1206–1208.

Kutcher S, Robertson HA, Bird D (1998): Premorbid functioning in adolescent onset bipolar I disorder: A preliminary report from an ongoing study. *J Affect Disord* 51:137–144.

Lapalme M, Hodgins S, LaRoche C (1997): Children of parents with bipolar disorder: A meta-analysis of risk for mental disorders. *Can J Psychiatry* 42:623–631.

Lewinsohn PM, Klein DN, Seeley JR (1995): Bipolar disorders in a community sample of older adolescents: Prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry* 34:454–463.

Lewinsohn PM, Klein DN, Seeley JR (2000): Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord* 2:281–293.

Manji HK, Chen G (2002): PKC, MAP kinases and the bcl-2 family of proteins as long-term targets for mood stabilizers. *Mol Psychiatry* 7:S46–S56.

Manji HK, Moore GJ, Chen G (2000): Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: Implications for the pathophysiology and treatment of manic-depressive illness. *Biol Psychiatry* 48:740–754.

McInnis MG, McMahon FJ, Chase GA, Simpson SG, Ross CA, DePaulo JR Jr (1993): Anticipation in bipolar affective disorder. *Am J Hum Genet* 53:385–390.

Nurnberger JI Jr, Berrettini W, Tamarkin L, Hamovit J, Norton J, Gershon E (1988): Supersensitivity to melatonin suppression by light in young people at high risk for affective disorder. A preliminary report. *Neuropsychopharmacology* 1:217–223.

Ongur D, Drevets WC, Price JL (1998): Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci U S A* 95:13290–13295.

Post RM (1992): Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry* 149:999–1010.

Radke-Yarrow M, Nottelmann E, Martinez P, Fox MB, Belmont B (1992): Young children of affectively ill parents: A longitudinal study of psychosocial development. *J Am Acad Child Adolesc Psychiatry* 31:68–77.

Robison LM, Skaer TL, Sclar DA, Galin RS (2002): Is attention deficit hyperactivity disorder increasing among girls in the US? Trends in diagnosis and the prescribing of stimulants. *CNS Drugs* 16:129–137.

Rosenberg DR, Sweeney JA, Squires-Wheeler E, Keshavan MS, Cornblatt BA, Erlenmeyer-Kimling L (1997): Eye-tracking dysfunction in offspring from the New York High-Risk Project: Diagnostic specificity and the role of attention. *Psychiatry Res* 66:121–130.

Sachs GS, Baldassano CF, Truman CJ, Guille C (2000): Comorbidity of attention deficit hyperactivity disorder with early- and late-onset bipolar disorder. *Am J Psychiatry* 157:466–468.

Soutullo CA, DelBello MP, Ochsner JE, McElroy SL, Taylor AA, Strukowski SM, et al (2002): Severity of bipolarity in hospitalized manic adolescents with history of stimulant or antidepressant treatment. *J Affect Disord* 70:323–327.

Strober M, Morrell W, Burroughs J, Lampert C, Danforth H, Freeman R (1988): A family study of bipolar I disorder in adolescence. Early onset of symptoms linked to increased familial loading and lithium resistance. *J Affect Disord* 15:255–268.

Wals M, Hillegers MH, Reichart CG, Ormel J, Nolen WA, Verhulst FC (2001): Prevalence of psychopathology in children of a bipolar parent. *J Am Acad Child Adolesc Psychiatry* 40:1094–1102.

Wehr TA, Sack D, Rosenthal N, Duncan W, Gillin JC (1983): Circadian rhythm disturbances in manic-depressive illness. *Fed Proc* 42:2809–2814.

Wozniak J, Biederman J, Kiely K, Ablon JS, Faraone SV, Mundy E, et al (1995a): Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry* 34:867–876.

Wozniak J, Biederman J, Mundy E, Mennin D, Faraone SV (1995b): A pilot family study of childhood-onset mania. *J Am Acad Child Adolesc Psychiatry* 34:1577–1583.

Young LT, Bakish D, Beaulieu S (2002): The neurobiology of treatment response to antidepressants and mood stabilizing medications. *J Psychiatry Neurosci* 27:260–265.

Zahn TP, Nurnberger JI Jr, Berrettini WH (1989): Electrodermal activity in young adults at genetic risk for affective disorder. *Arch Gen Psychiatry* 46:1120–1124.

Zahn-Waxler C, Mayfield A, Radke-Yarrow M, McKnew DH, Cytryn L, Davenport YB (1988): A follow-up investigation of offspring of parents with bipolar disorder. *Am J Psychiatry* 145:506–509.