A Prospective Study of the Offspring of Bipolar Parents Responsive and Nonresponsive to Lithium Treatment

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Background: The descriptions of clinical course among bipolar youths vary significantly and differ markedly from the findings described in classical studies of bipolar adults. This difference may in part reflect genetic heterogeneity. Response to lithium monotherapy identifies a homogeneous subgroup of bipolar adults. The aim of this study was to prospectively characterize the clinical course, including antecedent and comorbid conditions, among the offspring of 2 groups of bipolar parents divided on the basis of response to lithium.

Method: Parents were identified from families participating in ongoing molecular genetic studies and selected from specialty affective disorder clinics. For each child, 1 parent met Research Diagnostic Criteria/DSM-IV criteria for bipolar I disorder and either response or nonresponse to lithium prophylaxis. The other parent had no lifetime history of a major psychiatric illness. Blind to family affiliation and lithium response, all eligible offspring aged 10 to 25 years were interviewed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime Version (K-SADS-PL), and best-estimate diagnoses were made by a panel of experts. Offspring were then reassessed over a 5-year period.

Results: Offspring of lithium responders (N = 34) had good premorbid functioning and manifested classical mood disorders with an episodic course. Comorbid conditions in this group remitted prior to the mood disorder. In contrast, offspring of lithium nonresponders (N = 21) had poorer premorbid functioning and manifested mood disorders with a chronic course. Comorbid conditions continued alongside the mood disorder. Clinical course among affected offspring was predicted by the disease course of the parent.

Conclusion: The pattern of clinical course, remitting or nonremitting, appears to be inherited. Among the offspring of lithium-responsive bipolar parents, an early-onset subgroup with a classical episodic clinical course can be identified.

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A significant proportion of bipolar patients begin to experience their illness during adolescence, particularly if onset is defined as the first significant symptoms.[1] However, the majority of these patients suffer multiple mood episodes before being diagnosed, and this delay often has devastating and far-reaching consequences for their relationships, education, and employment.

Bipolar disorders run in families most likely on a genetic basis,[2] and the children of bipolar parents represent a group with an elevated risk for developing major affective disorders.[3] A number of high-risk studies have reported on the rate and the nature of psychopathology among the children of bipolar parents. Generally, most studies have found an elevated risk of psychopathology in the offspring of bipolar parents compared with that for the offspring of well controls or with rates of illness in the general population. However, there have been contradictory findings as to the nature of specific diagnoses across studies.

Specifically, in some high-risk studies there have been elevated rates of both internalizing (mood and anxiety) and externalizing (oppositional, conduct, attention-deficit/hyperactivity disorder [ADHD], and substance abuse) disorders with onset early in development and often presenting as comorbid.[4–12] These observations do not agree with classical studies of adult bipolar patients reporting normal premorbid functioning, onset after puberty, and low comorbidity.[1] However, other high-risk studies have

reported psychopathology clustering in the affective domain.[13–19] Factors contributing to the differences in high-risk studies may include assortative mating, developmental stage of the children, and heterogeneous parent samples.

With few exceptions, studies have not controlled for psychiatric morbidity in the nonaffected parent. Given the high degree of assortative mating, the observed variety of psychopathologic outcomes might reflect the manifestation of mixed bilineal genetic predisposition and/or a maladaptive response to the stress of having 2 ill parents, rather than representing a severe, atypical form of early-onset bipolar disorder as has been suggested.[20]

With regard to developmental stage, there are frequently reported differences in outcome between prepubertal versus older adolescent/young adult offspring samples. Specifically, among younger children, comorbidity is more often reported between mood and other major psychiatric illnesses (ADHD, anxiety, conduct), while in older high-risk cohorts, psychopathology is mostly accounted for by primary mood disorders. In one longitudinal study, anxiety disorders, substance abuse, and/or disruptive disorders appeared as antecedents to the development of full-blown mood disorders rather than as true (coexisting and independent) comorbid conditions.[13]

In order to understand the meaning of mixed psychopathology in young children from bipolar families, these children will need to be followed prospectively into adulthood. A few high-risk studies have included a follow-up component. Of these, Laroche et al.[16] reported a lack of continuity of disturbance over a 3- to 7-year follow-up period in school-aged offspring. Hammen et al.[10] reported few chronic, recurrent, or new onsets of psychiatric disturbance over 1 to 3 years among the school-aged offspring of bipolar, medically ill, or control mothers compared with high rates among the offspring of unipolar depressed mothers. Carlson and Weintraub[4] found that attentional and behavioral problems in early childhood were associated with a broad range of psychopathologic outcomes in adulthood, which included affective disorders.

By contrast, Akiskal et al.[13] have reported stability of affective diagnoses in adolescent and young adults at risk for bipolar disorder. Specifically, 79% of those with depression at the initial assessment had depressive recurrences during an average of 3 years of prospective follow-up. Moreover, 37.5% of those initially depressed developed a bipolar illness (bipolar I or II). Initial diagnoses of cyclothymia, dysthymia, and substance abuse predicted major affective disorder. These findings are in keeping with prospective studies of clinical and epidemiologic adolescent and young adult populations[21,22] and with longitudinal prospective studies of mood disorders in adults.[23]

Bipolar disorder is characterized by etiologic heterogeneity and variable phenotypic expression.[24] High-risk studies have so far not addressed these issues, which are recognized as key stumbling blocks in genetic studies and as directly relevant to high-risk studies. In the latter, the validity of the findings rests heavily on the accurate identification of the illness in the parent proband. We have attempted to reduce heterogeneity and improve diagnostic validity by selecting bipolar parent probands on the basis of a comprehensive clinical assessment taking into account the longitudinal clinical course and the exclusion of other illnesses.[25] We have also incorporated response to prophylactic lithium treatment to further reduce heterogeneity.[26] In previous studies, we have shown that an excellent response to long-term lithium prophylaxis is a clinical marker of a distinct, more homogenous subgroup of bipolar disorder characterized by an episodic course with good quality of remissions, a strong genetic loading, and a mode of transmission in keeping with a major gene effect.[2,27,28] Furthermore, in this patient population, we have reported an association and linkage to the phospholipase C gene[29] and strong linkage to chromosomal regions 15q14 and 7q11.[30]

A pilot study of the offspring of lithium-responsive and lithium-nonresponsive bipolar parents demonstrated clear differences in clinical course between the high-risk groups.[31] This suggested to us that it was useful to fully characterize and prospectively study more homogeneous high-risk populations. In this way, reported differences in clinical characteristics of unselected heterogeneous populations of mood-disordered adolescents could be clarified. In this article, we describe the premorbid functioning, onset of illness, clinical course, comorbidity, and the relationship to the parent's illness in 2 groups of at-risk offspring, divided on the basis of their parent's lithium response. This work was based on over 5 years of repeated, prospective clinical follow-up.

METHOD

Families

Parents were identified from families participating in ongoing molecular genetic studies and selected from specialty affective disorder clinics at the Royal Ottawa and Hamilton Psychiatric hospitals. Probands were all followed prospectively and met Research Diagnostic Criteria (RDC)/DSM-IV criteria for bipolar I disorder and an unequivocal response or nonresponse to long-term lithium monotherapy (see below). In 4 cases, we included an affected (recurrent major depression N = 3; bipolar II N = 1) relative (sister) of a lithium-responsive bipolar I proband as a parent in this study. We included these 4 cases because in our opinion they suffer from a bipolar disorder: their illness has a typical bipolar profile with early onset and frequently recurring and remitting mood episodes, and their family history contains only members with lithium-responsive bipolar disorders. In all included

families, the other biological parent had no lifetime history of a major affective disorder, schizophrenia, or schizoaffective disorder on the basis of a Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L)[32] interview. The families had to have at least 1 offspring between the ages of 10 and 25 years at inclusion.

Parent Diagnostic Assessments

As part of a larger molecular genetic study, all parents, spouses, and available first-degree relatives were interviewed in a blind fashion by pairs of experienced research clinicians using SADS-L interview format. Final RDC/DSM-IV diagnoses and illness parameters (age at onset, clinical course) were decided using all available clinical material in a blind consensus fashion by an independent panel of senior clinical researchers. There was no incidence of disagreement with regard to proband diagnosis or lithium response.

Lithium Response

All probands had to have met research criteria for a clear response or nonresponse to lithium monotherapy as described in previous reports.[30,33] Briefly, all probands had to have a highly recurrent illness course prior to treatment with lithium. Lithium responders had to have no recurrences of illness during a minimum of 3 years of adequate lithium monotherapy (plasma levels > 0.7 mmol/L). Lithium nonresponders had to have at least 2 illness recurrences while on adequate lithium treatment (as documented by a therapeutic plasma level at the time of relapse).

Offspring Assessment

All families giving informed consent with offspring aged 10 to 25 years were included in the study. An effort was made to recruit as many offspring from consenting families as possible, independent of their clinical state. The offspring completed a Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime Version (K-SADS-PL)[34] interview conducted by a child psychiatrist (A.D.) blind to family affiliation and parental lithium response. Either one or both parents were interviewed separately about each child. DSM-IV diagnoses were made in a blind fashion on the basis of all available clinical material by a panel of senior research psychiatrists (S.K., P.G., M.A.). There was only 1 case of disagreement regarding diagnosis, and this adolescent was reinterviewed blindly by a second psychiatrist and a consensus was reached.

After the first baseline assessment, all consenting/assenting offspring were reinterviewed at least once during the next 5 years following K-SADS-PL format by the same child psychiatrist. In follow-up interviews, emphasis was placed on the interval between the first and subsequent assessments. In most cases, at least 1 parent was reinterviewed about each child. In all cases, decisions about diagnosis and clinical course were made on a blind consensus basis among a panel of expert senior psychiatrists using all available clinical material. This study is a naturalistic prospective follow-up, and therefore this report does not describe treatment outcomes. Issues pertaining to treatment in this population will form the subject of a future separate publication.

Statistical Analysis

The groups were compared using chi-square analysis (with Yates correction where appropriate), the Fisher exact test, and t tests. For evaluating the factors contributing to the risk of illness, we used the Cox proportional hazards model.

RESULTS

Sample Description

We are reporting on 55 subjects who completed baseline assessments: 34 offspring from 19 lithium-responder families and 21 offspring from 11 lithium-nonresponder families. Forty-five of these offspring, 26 (76%) from lithium-responder families and 19 (90%) from lithium-nonresponder families, were prospectively reassessed once or several times as described above at the time of this report. There were no differences in demographic data or affected status between those offspring remaining to be reassessed and those with at least 1 follow-up interview. Baseline assessments on 36 offspring (21 of lithium responders and 15 of lithium nonresponders) were originally described in an earlier brief report.[31]

There were no differences in age at onset, number of lifetime episodes, or sex ratio between parent groups. However, a lifetime history of psychotic symptoms was less frequent among lithium-responsive parents compared with lithium-nonresponsive parents ($\chi^2 = 8.80$, df = 2, $p = .01$). Further, lithium-responsive parents tended to have episodic illnesses as compared with lithium-nonresponsive parents, who tended to have nonremitting illnesses characterized by significant residual or chronic fluctuating symptoms ($\chi^2 = 22.09$, df = 2, $p < .001$). For the lithium-responsive probands, the mean number of lifetime episodes prior to lithium was 9.25, and 67% required hospitalization at some point in their prelithium course. The mean duration of lithium treatment was 14.25 years.

There were no statistically significant differences in the mean ± SD age at the baseline assessment (18 ± 5 years vs. 16 ± 4 years), the male:female sex ratio (15:19 vs. 6:15), or the lifetime prevalence of an affective disorder (10/34 vs. 10/21) or of any other psychiatric illness (9/34 vs. 10/21) between the offspring of lithium responders and the offspring of lithium nonresponders, respectively. The mean length of prospective follow-up was also

Table 1. Quality of Early Childhood Functioning Among the Offspring of Bipolar Patients

Level of Functioning	Offspring of Lithium Responders (N = 34)		Offspring of Lithium Nonresponders (N = 21)	
	N	%	N	%
Poor functioning	0	0	7	33
Normal functioning	10	29	9	43
Gifted	24	71	5	24

comparable between the groups (27 ± 18 months vs. 35 ± 18 months, offspring of lithium responders vs. offspring of lithium nonresponders, respectively).

Early Childhood Functioning

On the basis of a blind consensus review of parent and offspring data, the quality of functioning during early childhood (up to age 10) was ranked as poor, normal, or gifted. A poor ranking required clear evidence of significant psychiatric symptoms, associated difficulty in functioning (academically and/or socially), and some form of professional assessment or intervention. Normal functioning was considered adequate competence in school and social roles (with peers and at home) with no psychiatric/psychological intervention. Gifted status was judged on the basis of external validation (awards, gifted programs) of outstanding achievement in at least 1 of 4 areas: academics, athletics, art, or leadership.

There were significant differences between the groups with regard to the quality of childhood functioning (Table 1). Essentially, the offspring (affected and unaffected) of lithium responders tended to have a good quality of early functioning, often being characterized as gifted. By comparison, a significant number of the offspring of lithium nonresponders had an abnormal early childhood course marked by psychiatric symptoms associated with major problems in academic and/or social functioning ($\chi^2 = 16.63$, df = 2, p = .0002). Only 1 of the 10 affected offspring of lithium nonresponders had an early developmental course characterized as gifted compared with 6 of the 10 affected children of lithium responders ($\chi^2 = 5.49$, df = 1, p = .057).

Psychopathology

The lifetime psychiatric diagnoses for the entire offspring sample are presented in Table 2. There was no difference in the rate of lifetime psychiatric disorders, including affective disorders, between the offspring of lithium responders and lithium nonresponders. However, among the offspring of lithium responders there was no occurrence of cluster A personality disorders or schizoaffective disorders, unlike the comparison group. The most prevalent affective diagnosis was depressive disorder in both groups (6/10 among the offspring of lithium responders and 7/10 among the offspring of lithium nonresponders).

Table 2. Lifetime DSM-IV Psychiatric Diagnoses Among the Offspring of Bipolar Parents[a]

DSM-IV Diagnosis	Offspring of Lithium Responders (N = 34)	Offspring of Lithium Nonresponders (N = 21)
Bipolar disorder type I, II, or NOS	4	1
Major depressive disorder	4	6
Minor depressive disorder	2	1
Dysthymic disorder	0	2
Cyclothymic disorder	0	1
Schizoaffective disorder	0	1
Cluster A personality disorder	0	3
Anxiety disorder	4	4
Substance use disorder	2	4
Oppositional defiant disorder	0	1
Adjustment disorder	1	0
Attention-deficit/hyperactivity disorder with learning disability	0	2
Sleep disorder	2	2
Unaffected	19	9

[a]Some individuals have more than 1 lifetime diagnosis. Abbreviation: NOS = not otherwise specified.

Onset of Affective Illness

In both groups, offspring tended to manifest DSM-IV mood disorders during mid-adolescence (16.8 ± 4.9 years for offspring of lithium responders vs. 14.6 ± 3.8 years for offspring of lithium nonresponders). However, in the year prior to the onset of the mood disorder, 9 of 10 offspring of lithium responders were well with no significant psychiatric symptoms, while all 10 offspring of lithium nonresponders were experiencing significant psychiatric symptoms with evidence of impairment in functioning ($\chi^2 = 16.36$, df = 1, p = .0001). Among the affected offspring of lithium responders, in all cases the index mood episode was an abrupt onset of depression (7 major depressive episodes, 2 with mood-congruent psychotic symptoms; 3 brief minor depressive episodes). By contrast, among the affected offspring of lithium nonresponders, 9 experienced a gradual onset of the mood disorder (2 dysthymia, 1 cyclothymia, 1 minor depressive, and 5 major depressive episodes) after an extended period of chronic fluctuating psychiatric symptoms including mood lability, substance abuse, anxiety, and/or cluster A traits. The 1 remaining affected offspring of lithium nonresponders had an abrupt onset of a depressive episode superimposed on a chronic anxiety disorder.

Clinical Course of Affective Illness

Despite relatively small numbers of affectively ill offspring, there were clear differences between the groups with respect to the course of illness (Table 3). Nine of 10 affected offspring of lithium responders experienced complete remissions of mood episodes, while the remaining offspring of lithium responders experienced significant

Table 3. Course of Illness in Affectively Ill Offspring

Course	Offspring of Lithium Responders (N = 10)	Offspring of Lithium Nonresponders (N = 10)
Episodic	9	1
Episodic-residual	1	3
Chronic-fluctuating	0	5
Chronic	0	1

residual symptoms between episodes. By comparison, only 1 of 10 affected offspring of lithium nonresponders experienced complete remission of episodes ($\chi^2 = 12.80$, df = 1, p = .001). Statistically, the comparison between those offspring experiencing complete remissions versus those with residual, chronic fluctuating, or chronic symptoms was significantly different between the groups ($\chi^2 = 13.4$, df = 3, p = .004).

In both high-risk groups, affective illnesses tended to either recur or persist over the follow-up period. Among the 9 of 10 affected offspring of lithium responders prospectively reassessed, 7 experienced new episodes and 2 remained in complete remission. Comparatively, among the 10 prospectively assessed affected offspring of lithium nonresponders, 9 experienced active illness during the follow-up period in the form of either new episodes with residual symptoms (N = 3), chronic-fluctuating symptoms (N = 5), or persistence of the index major depressive episode (N = 1). One lithium-nonresponder offspring with a history of recurrent major depression at baseline remained in remission throughout the follow-up period.

Comorbid Illnesses in Affectively Ill Offspring

There was no statistically significant difference between the groups in the rate of other lifetime psychiatric illness among those with an affective diagnosis ($\chi^2 = 1.88$, df = 1, p = .17). However, there was a tendency for comorbidity to be higher among the affectively ill offspring of lithium nonresponders.

Although numbers are small, there was a significant difference noted in the nature of comorbidity between offspring groups ($\chi^2 = 5.99$, df = 2, p = .03) (Table 4). Comorbid illnesses among the affectively ill offspring of lithium responders tended to have onset and remit prior to the onset of the mood disorder (sequential comorbidity). Specifically, during early childhood, 1 individual experienced panic disorder with agoraphobia and 2 offspring experienced a sleep disorder, all of which remitted years prior to the onset of the mood disorder. There was 1 affectively ill offspring of a lithium responder who persistently met criteria for a substance use disorder after the onset of and between mood episodes. It is of note that 2 additional offspring of lithium responders, who have not yet developed a mood disorder, have experienced an abrupt onset and complete remission of an anxiety disorder (phobia to mushrooms and panic disorder, respectively).

Table 4. Comorbidity Among the Affectively Ill Offspring

Type of Comorbidity	Offspring of Lithium Responders (N = 10)	Offspring of Lithium Nonresponders (N = 10)
None	6	2
Sequential	3	1
Concurrent	1	7

By comparison, the affectively ill offspring of lithium nonresponders tended to develop comorbid illnesses prior to the onset of the mood disorder that, in most cases, persisted alongside the mood disorder (concurrent comorbidity). The profile of comorbid disorders in this group was as follows: 2 concurrent anxiety disorders; 1 concurrent anxiety disorder, substance use disorder, and learning disability; 1 concurrent anxiety disorder and substance use disorder; 1 substance use disorder; 1 schizotypal personality disorder; 1 sleep disorder; and 1 concurrent sleep disorder and schizotypal personality disorder.

Finally, the heavy use of substances (mostly alcohol and marijuana) was associated with mood episodes in both of the high-risk groups. Among the offspring of lithium responders, 6 used substances during acute episodes, although only 1 individual met diagnostic criteria for a comorbid substance abuse disorder. By comparison, 4 of the affectively ill offspring of lithium nonresponders used substances heavily, and 3 of these individuals met diagnostic criteria for a substance use disorder.

Associated/Predictive Factors

In a survival analysis (Cox proportional hazard), the risk of affective disorders among the offspring of lithium nonresponders was significantly associated with having an affected mother (p = .03), poor early childhood functioning (p = .048), and, to some extent, with chronicity of illness in the affected parent (p = .067). On the other hand, affective illness among the offspring of lithium responders was not predicted by any of the covariates tested, including sex, parent sex, other illnesses, premorbid course, parent age at onset, parent course, and psychotic symptoms in parent course. The age at onset for the parent was not associated with the age at onset in the affected child. There was a strong association between the course of illness in the parent and the course of illness in the affected child ($\chi^2 = 21.89$, df = 6, p = .001) (Table 5). A lifetime history of psychotic symptoms in the parent did not predict the course of illness in the child.

DISCUSSION

The major finding in this prospective, longitudinal follow-up study was a robust difference in the clinical course between the affected offspring of lithium-responsive and lithium-nonresponsive bipolar parents. Parents with a classical episodic bipolar disorder characterized by complete remissions and an excellent response

Table 5. Course of Affective Disorders Between Offspring and Parent

	Parent Course			
Offspring Course	Episodic	Episodic-Residual	Chronic-Fluctuating	Chronic
Episodic	9	0	1	0
Episodic-residual	1	1	2	0
Chronic-fluctuating	0	5	0	0
Chronic	0	1	0	0

to lithium tended to have children who developed typical, episodic affective disorders. These offspring could be termed the "classical" early-onset subgroup.

Affective disorders among the offspring of lithium responders tend to have abrupt onset superimposed on a normal or gifted premorbid development. Affective disorders in this high-risk group tend to remit and recur with good quality of remissions. Antecedent conditions in this subgroup were sleep and anxiety disorders, appearing episodically and remitting prior to the onset of the mood disorder. Other groups have described a high prevalence of anxiety disorders preceding the onset of bipolar disorder in youths.[35] These symptoms/syndromes may represent the first manifestation of the underlying bipolar disorder determined by developmental stage and/or the stage of the clinical course.

By contrast, parents with a bipolar illness characterized by incomplete remissions tended to have children who manifested significant problems in social and/or academic functioning early in childhood prior to the onset of a diagnosable mood disorder. Antecedent psychiatric symptoms in these children tended to continue alongside the mood disorder, which itself followed a chronic course with poor quality of remission. These offspring could be termed the "nonclassical" early-onset subgroup. Affective disorder in this high-risk cohort was predicted by the female sex of the affected parent and poor premorbid functioning in the child.

It does not appear that the differences in outcome between offspring groups are attributable to the psychosocial stress of having a more ill parent. For example, among the lithium-responder families, probands had a highly recurrent illness course, often requiring hospitalization prior to lithium treatment. Further, all families had a second parent who did not suffer from a major psychiatric illness.

These results help to clarify the differences between the studies of adults with primary recurrent affective disorders and more recent studies of very young mood-disordered children. Essentially, the former studies demonstrated that adults with bipolar disorders had normal premorbid personality profiles and good psychosocial functioning with a remitting and recurrent illness course, while the latter studies have described a group of severely disturbed, chronically ill children, often characterized by a predominately irritable mood and bizarre behavior.[36–38] Our results show that narrowly defined, classical episodic bipolar disorder runs in families and, further, that more broadly defined bipolar disorder seems to identify a different population of patients who suffer from a variety of incompletely remitting psychiatric disorders likely overlapping with psychotic spectrum illnesses.

Our findings are also in agreement with other studies of remitted bipolar youths, which have reported evidence of good to excellent social and academic functioning prior to the onset of the mood disorder on review of school records and by parental report.[39,40] Further, the differences in early childhood functioning and clinical course between our high-risk groups are similar to the differences described in studies comparing bipolar and schizophrenic children.[41]

There are several limitations of this study. First, studying specialized populations limits the generalizability of the results. However, in order to understand the etiology, interplay between risk factors, course of illness, and treatment response in bipolar disorder, we need to study homogeneous subgroups. In support of this view, we have found clear differences between high-risk groups even though to date our sample size is relatively small. In addition, there is a retrospective component to this prospective high-risk study, as the offspring were not always interviewed prior to the onset of their first episode. In addition, the characterization of early childhood functioning was based on retrospective history of the parent and child. Despite this, we feel that our results are valid. We based our findings on direct, repeated prospective clinical interviews reviewed on a blind consensus basis with a panel of clinical research experts. For retrospective history prior to the first baseline assessment, we interviewed the child and at least 1 parent. We reviewed all available clinical material, including patient charts. As well, we required external validating information to determine the quality of early childhood functioning, including intervention by a health professional and evidence of impairment (poor) on the one hand and evidence of awards, achievements, and/or enrichment programs on the other.

From our findings, we speculate that most of the affected offspring of lithium-responsive probands will themselves respond to long-term lithium prophylaxis. This hypothesis is based on our observations of a high degree of lithium responsivity among the affected adult family members of lithium-responsive probands compared with response rates among family members of a sample of unselected bipolar patients.[42] Further, affected offspring of lithium responders have characteristics known to predict a good response to lithium among affected adults, including an episodic course, good quality

of remissions, and normal premorbid functioning.[33] This was a naturalistic follow-up study, and despite significant illness (severe episodes and high relapse rates), none of the affected offspring were in systematic ongoing treatment. We are now piloting an open trial of lithium prophylaxis among the offspring affected with recurrent mood disorders.

We further hypothesize that the activity of the underlying affective illness among the children of lithium responders may first become clinically apparent as an episode of significant psychiatric symptoms that then remits. We do not see the abrupt onset and complete remission of an anxiety disorder or sleep disorder in this population as true comorbidity in the sense of an independent, coexisting illness. Rather, we hypothesize that these conditions may be antecedents to the onset of the full-blown disorder, and the variable phenotypic expression may be reflective of differences in course or developmental stage rather than due to a different underlying disease process. Prospective longitudinal studies among these high-risk offspring of neuroendocrine parameters associated with established illness in well-characterized bipolar adults (e.g., cortisol hypersecretion[43]) will begin to address this hypothesis.

REFERENCES

1. Goodwin FK, Jamison KR. Childhood and adolescence. In: Manic-Depressive Illness. New York, NY: Oxford University Press; 1990: 186–209
2. Alda M. Bipolar disorder: from families to genes. Can J Psychiatry 1997; 42:378–387
3. Duffy A. Toward effective early intervention and prevention strategies for major affective disorders: a review of antecedents and risk factors. Can J Psychiatry 2000;45:340–348
4. Carlson GA, Weintraub S. Childhood behavior problems and bipolar disorder: relationship or coincidence? J Affect Disord 1993;28:145–153
5. Chang KD, Steiner H, Ketter T. Psychiatric phenomenology of child and adolescent bipolar offspring. J Am Acad Child Adolesc Psychiatry 2000; 39:453–460
6. Decina P, Kestenbaum CJ, Farber S, et al. Clinical and psychological assessment of children of bipolar probands. Am J Psychiatry 1983;140: 548–553
7. Gershon ES, McKnew D, Cytryn L, et al. Diagnoses in school-age children of bipolar affective disorder patients and normal controls. J Affect Disord 1985;8:283–291
8. Grigoroiu-Serbanescu M, Christodorescu D, Jipescu I, et al. Psychopathology in children aged 10–17 of bipolar parents: psychopathology rate and correlates of the severity of the psychopathology. J Affect Disord 1989;16:167–179
9. Hammen C, Gordon D, Burge D, et al. Maternal affective disorders, illness, and stress: risk for children's psychopathology. Am J Psychiatry 1987;144:736–741
10. Hammen C, Burge D, Burney E, et al. Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder. Arch Gen Psychiatry 1990;47:1112–1117
11. Radke-Yarrow M, Nottelmann ED, Martinez P, et al. Young children of affectively ill parents: a longitudinal study of psychosocial development. J Am Acad Child Adolesc Psychiatry 1992;31:68–77
12. Zahn-Waxler C, Mayfield A, Radke-Yarrow M, et al. A follow-up investigation of offspring of parents with bipolar disorder. Am J Psychiatry 1988; 145:506–509
13. Akiskal HS, Downs J, Jordan P, et al. Affective disorders in referred children and younger siblings of manic-depressives: mode of onset and prospective course. Arch Gen Psychiatry 1985;42:996–1003
14. Klein DN, Depue RA, Slater JF. Cyclothymia in the adolescent offspring of parents with bipolar affective disorder. J Abnorm Psychol 1985;94: 115–127
15. Laroche C, Cheifetz P, Lester EP, et al. Psychopathology in the offspring of parents with bipolar affective disorders. Can J Psychiatry 1985;30: 337–343
16. Laroche C, Sheiner R, Lester E, et al. Children of parents with manic-depressive illness: a follow-up study. Can J Psychiatry 1987;32:563–569
17. Nurnberger J, Hamovit J, Hibbs ED, et al. A high risk study of primary affective disorder: selection of subjects, initial assessment, and one-to-two year follow-up. In: Dunner D, Gershon E, Barrett J, eds. Relatives at Risk for Mental Disorders. New York, NY: Raven Press Ltd; 1988:161–177
18. Todd RD, Reich W, Petti TA, et al. Psychiatric diagnoses in the child and adolescent members of extended families identified through adult bipolar affective disorder probands. J Am Acad Child Adolesc Psychiatry 1996; 35:664–671
19. Waters BG, Marchenko-Bouer I. Psychiatric illness in the adult offspring of bipolar manic-depressives. J Affect Disord 1980;2:119–126
20. Geller B, Luby J. Child and adolescent bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 1997;36:1168–1176
21. Strober M, Schmidt-Lackner S, Freeman R, et al. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. J Am Acad Child Adolesc Psychiatry 1995;34:724–731
22. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. J Am Acad Child Adolesc Psychiatry 1995;34:454–463
23. Angst J. The course of affective disorders. Psychopathology 1986;19 (suppl):47–52
24. Alda M, Grof P. Genetics and lithium response in bipolar disorders. In: Soares JC, Gershon S, eds. Basic Mechanisms and Therapeutic Implications of Bipolar Disorder. New York, NY: Marcel Dekker; 2000:529–543
25. Grof P, Alda M, Ahrens B. Clinical course of affective disorders: were Emil Kraepelin and Jules Angst wrong? Psychopathology 1995;28:73–80
26. Grof P, Alda M, Grof E, et al. Lithium response and genetics of affective disorders. J Affect Disord 1994;32:85–95
27. Smeraldi E, Petroccione A, Gasperini M, et al. Outcomes on lithium treatment as a tool for genetic studies in affective disorders. J Affect Disord 1984;6:139–151
28. Alda M, Grof P, Grof E, et al. Mode of inheritance in families of patients with lithium-responsive affective disorders. Acta Psychiatr Scand 1994; 90:304–310
29. Turecki G, Grof P, Cavazzoni P, et al. Evidence for a role of phospholipase c-γ1 in the pathogenesis of bipolar disorder. Mol Psychiatry 1998;3: 534–538
30. Turecki G, Grof P, Grof E, et al. Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. Mol Psychiatry 2001;6:570–578
31. Duffy A, Alda M, Kutcher S, et al. Psychiatric symptoms and syndromes among adolescent children of parents with lithium-responsive or lithium-nonresponsive bipolar disorder. Am J Psychiatry 1998;155:431–433
32. Spitzer RL, Endicott J. Schedule for Affective Disorders and Schizophrenia-Lifetime Version. New York, NY: Biometric Research, New York State Psychiatric Institute; 1979
33. Grof P, Alda M, Grof E, et al. The challenge of predicting response to stabilizing lithium treatment: the importance of patient selection. Br J Psychiatry 1993;163(suppl 21):16–19
34. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36:980–988
35. Masi G, Toni C, Perugi G, et al. Anxiety disorders in children and adolescents with bipolar disorder: a neglected comorbidity. Can J Psychiatry 2001;46:797–802
36. Faraone SV, Biederman J, Mennin D, et al. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? J Am Acad Child Adolesc Psychiatry 1997;36:1378–1390
37. Wozniak J, Biederman J, Kiely K, et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry 1995;34:867–876
38. Geller B, Fox LW, Clark KA. Rate and predictors of prepubertal bipolarity during follow-up of 6-to 12-year-old depressed children. J Am Acad Child Adolesc Psychiatry 1994;33:461–468
39. Quackenbush D, Kutcher S, Robertson HA, et al. Premorbid and

postmorbid school functioning in bipolar adolescents: description and suggested academic interventions. Can J Psychiatry 1996;41:16–22
40. Kutcher S, Robertson HA, Bird D. Premorbid functioning in adolescent onset bipolar I disorder: a preliminary report from an ongoing study. J Affect Disord 1998;51:137–144
41. Werry JS, McCellan JM, Chard L. Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: a clinical and outcome study. J Am Acad Child Adolesc Psychiatry 1991;30:457–465
42. Grof P, Alda M, Duffy A, et al. Treatment response in the relatives of lithium responders [abstract]. Int J Neuropsychopharmacol 2000;3 (suppl 1):339
43. Goodyer IM, Park RJ, Netherton CM, et al. Possible role of cortisol and dehydroepiandrosterone in human development and psychopathology. Br J Psychiatry 2001;179:243–249