Early-Onset Bipolar Disorder and Treatment Delay Are Risk Factors for Poor Outcome in Adulthood

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Objective: We examined the influence of age at onset of illness and the delay in time to first treatment on morbidity in adulthood.

Method: 529 adult outpatients with a mean age of 42 years, who entered our research network from 1996 through 2001 and who were diagnosed with bipolar disorder according to *DSM-IV* criteria, were rated prospectively on a daily basis with the National Institute of Mental Health-Life Chart Method during naturalistic treatment for up to 4 years.

Results: Fifty percent of patients had illness onset in childhood (< 13 years of age) or adolescence (13–18 years of age). In year 1 of follow-up, these patients, compared to those with adult onset, showed significantly ($P < .05$) greater severity of depression and mania, greater number of episodes, more days depressed, more days of ultradian cycling, and fewer days euthymic. After 4 years, the mean severity and duration of depression remained greater and the number of days euthymic fewer in those with childhood compared to adult onset ($P < .05$). The delays to first treatment correlated inversely with age at onset of illness. Independently, delay to first treatment was associated with more time depressed, greater severity of depression, greater number of episodes, more days of ultradian cycling, and fewer days euthymic (all $P < .05$).

Conclusions: These data converge with other evidence that onset of bipolar disorder in childhood is common and often associated with extraordinarily long delays to first pharmacologic treatment. Both childhood onset and treatment delay were associated with a persistently more adverse course of illness rated prospectively in adults. These data should help foster efforts to ensure earlier and more effective treatment of bipolar illness in children and adolescents. It is hoped that appropriate early intervention would result in a more benign illness and a better prognosis in adulthood.

J Clin Psychiatry 2010;71(7):864–872

Submitted: *December 22, 2008; accepted June 9, 2009 (doi:10.4088/JCP.08m04994yel).*
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Bipolar disorder can remain undiagnosed and untreated for many years, especially when it has an early age at onset or is associated with multiple comorbidities. We previously reported that 50% of adult outpatients had childhood-onset and adolescent-onset illness, these were associated with long delays to first treatment compared to patients with adult-onset illness, and those with early-onset illness ultimately had a variety of measures of poor outcome as adults.[1,2]

Perlis et al[3] have also looked at age at onset and outcome. They divided their adult bipolar cohort from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) program into childhood onset (age 0–12 years), adolescent onset (age 13–18 years), early adult onset (age 19–29 years), and late adult onset (age 30 years and older). They reported that 28% of their patients had illness onset in childhood and that a total of 66% had an onset prior to age 19. They also found that early illness onset was associated with a variety of measures of poor outcome, including greater number of episodes and more suicide attempts, as well as substance abuse and anxiety comorbidity.[3]

In our initial report,[2] we observed many of these same retrospective indices of poor outcome. Additionally, these retrospective patient observations were validated by clinician ratings in the first year of prospective follow-up during naturalistic treatment.[2] Compared with adult-onset cases, those with childhood-onset and adolescent-onset bipolar illness had greater severity of mania and depression, more episodes, and fewer days euthymic in the first year of follow-up. In that brief report,[2] we were not able to present a variety of important and more detailed aspects of the data, which we now address in this article.

Many of our patients were followed into a second, third, and fourth year of prospective assessment, and their long-term follow-up data are also reported here. While we found that early-onset illness was inversely proportional to the degree of delay to first treatment with pharmacotherapy for mania or depression, left unaddressed was how this delay in onset to first treatment varied as a function of the polarity of the first episode (mania versus depression) and how the delay to first treatment itself might have been independently associated with prospective outcome measures.

In this article, we explore these and additional relationships of the separate contributions that both age at onset and delay to first treatment might have on the persistently poor prognosis observed in longer-term follow-up of adults who had the earliest onset of bipolar disorder. The duration of untreated illness in schizophrenia has been shown in a recent meta-analysis[4] to relate to severity of negative symptoms. If similar, poor long-term outcomes were associated with a longer duration of time to first treatment in bipolar illness,

For Clinical Use

- Compared with adult-onset bipolar disorder, childhood- and adolescent-onset bipolar disorder are associated with a more difficult course of illness, both retrospectively assessed and prospectively rated in adults of an average age of 42 years.
- Younger age at onset of bipolar disorder is inversely correlated with longer delay to first treatment for mania or depression.
- The length of delay to first treatment of bipolar disorder is independently related to more time depressed, greater severity of depression, and less time euthymic in prospectively rated adults
- Treatment delay is a remediable risk factor for poor outcome in childhood-onset bipolar disorder; earlier intervention might yield a more benign illness course.

this would suggest that the delay could be a modifiable prognostic factor in both of the major psychoses and that the attempts at early or prodromal intervention that are now prominent for schizophrenia would deserve further clinical and public health attention in bipolar illness as well.

METHOD

The methods involved in this adult outpatient cohort are presented in detail elsewhere.[1,5–9] Briefly, all patients participated in an outpatient network in which there were few exclusions from participation other than active substance abuse requiring treatment at another facility, or very severe comorbid medical problems that would preclude the potential for participation in treatment protocols.[5]

Patients gave oral and written informed consent for participation in the network, as approved by the institutional review board at each local institution. They were formally diagnosed using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID), and they completed questionnaires about the extent of their prior course of illness. Age at onset was recorded for the first depressive symptoms associated with dysfunction and the first hypomanic or manic symptoms presenting similarly to those occurring in adulthood, as well as age at first pharmacologic treatment for either mania or depression. Demographic and clinical characteristics of the population are reported elsewhere,[2] but the mean age at network entry was 42 years. Patients were treated essentially naturalistically without a placebo during comparative clinical trials, except in the instance of a comparison of adjunctive omega free fatty acid versus placebo.[10] Patients were entered into the network from 1996 through 2001.

Upon network entry, patients were assessed prospectively on a variety of cross-sectional measures and had daily prospective National Institute of Mental Health-Life Chart Method (NIMH-LCM)[11–13] ratings for severity of mania or depression between clinic visits, which ranged from weekly to monthly depending on severity of the patient's symptomatology. These prospective NIMH-LCM ratings[11] have been validated against cross-sectional measures and have been found to be highly reliable over these relatively short time intervals.[12,13] Mood phase switches occurring 1 or more times within a day (ie, ultradian cycling) were also noted separately, although these shifts were not counted in the determination of the number of episodes meeting *DSM-IV* criteria.[9]

All patients included in this analysis had at least 1 full year of prospective daily clinician ratings, and fewer patients were available in the second, third, and fourth years of follow-up and treatment. Normality for continuous measures was examined using the Kolmogorov-Smirnov test. All P values were evaluated for significance at $P < .05$, 2-tailed.

Linear mixed models with restricted maximum likelihood estimation were used to examine the course of illness over 4 years of follow-up by onset group. A random intercept for the patient was included using variance components. Schwarz's Bayesian criterion was used to determine the best-fitting covariance structure: a first-order autoregressive structure. Separate models were run for depression severity, days of depression, mania severity, days of mania, *DSM-IV* episodes, days well, and days of ultradian cycling. Bonferroni-corrected pairwise comparisons ($\alpha < .05$) were used post hoc to examine omnibus effects. All post hoc comparisons are reported following correction except as noted.

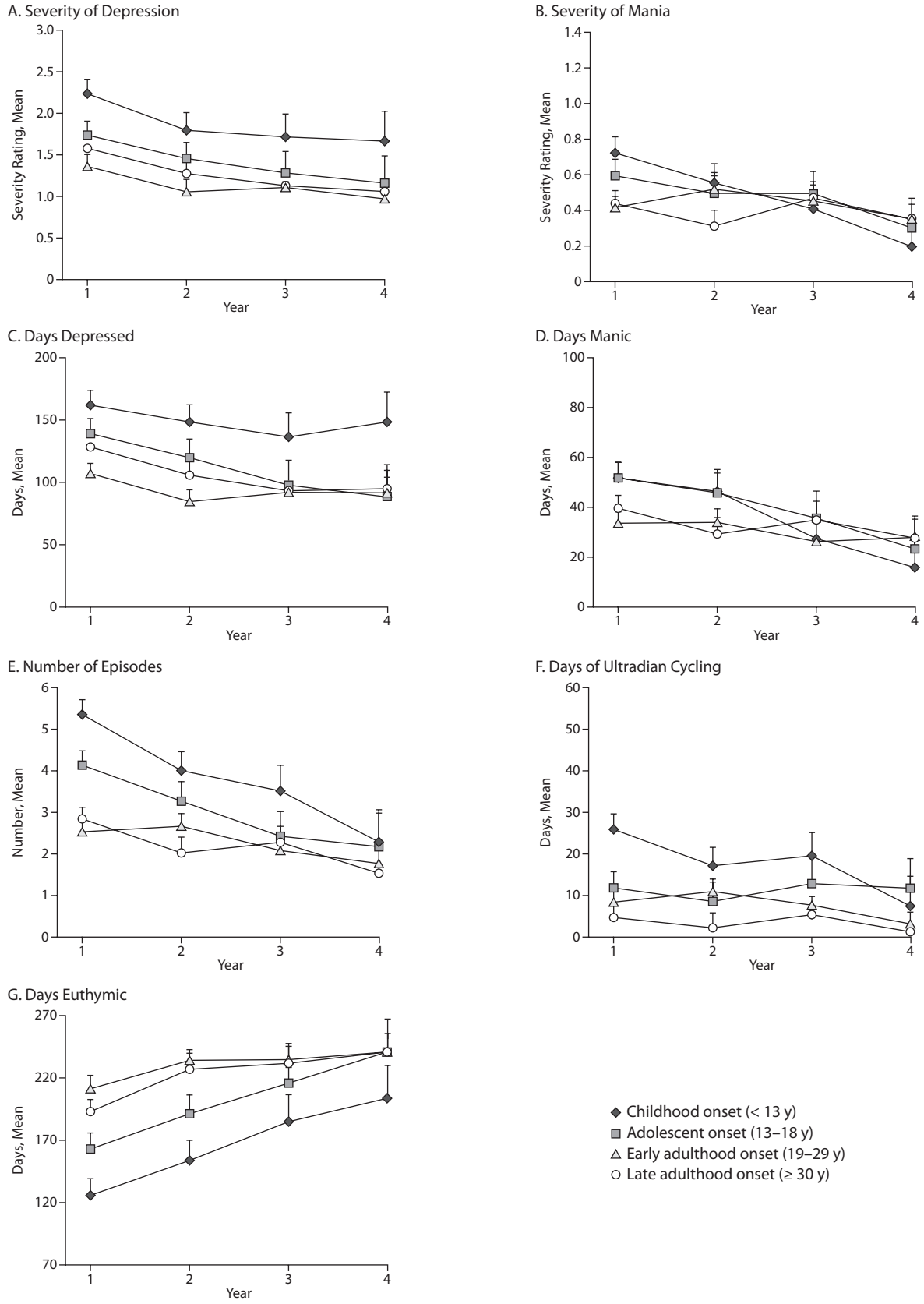
Pearson correlations were used to examine the relationship between age at onset and delay to first treatment with each outcome measure. The relationship between age at onset and delay to first treatment was examined in the sample as a whole and separately for groups with different mood states (polarity) at first episode as well as in different age cohorts. Once these relationships were established, linear regression analysis was performed using age at onset and delay to first treatment as predictors of outcome to determine whether they had independent contributions to illness outcomes assessed in the first year of prospective ratings.

RESULTS

Early Age at Onset and Sustained Poor Prognosis Through the Fourth Year of Follow-Up

Fifteen percent of patients with bipolar illness in this adult outpatient cohort had onset prior to age 13, and 35% had onset as adolescents (aged 13 to 18 years), such that 50% of the patients had their first episodes of illness in childhood or adolescence.[2] Figure 1 shows the prospective outcomes in the first (n = 480), second (n = 293), third

Figure 1. Prospective Outcome in Adults With Bipolar Disorder in the First (n = 480), Second (n = 293), Third (n = 181), and Fourth (n = 137) Years of Treatment as a Function of Grouping by Age at Onset of Illness[a,b]



[a]Prospective clinician ratings using the National Institute of Mental Health-Life Chart Method show a persistently poor outcome for severity and duration of depression and number of days euthymic in those with childhood-onset illness over the 4 years of prospective follow-up.
[b]Vertical bars indicate 1 standard error of the mean.

Table 1. Significance of Prospective Outcome Measures as a Function of Age-at-Onset Group[a]

	Linear Mixed Models								
	Time in Network[b]			Group by Age at Onset of Bipolar Disorder[c]			Interaction of Time × Onset[d]		
Adult Outcome Measure	*F*	*df*	*P*	*F*	*df*	*P*	*F*	*df*	*P*
Depression									
Severity	11.36	3,523	<.0001	3.44	3,572	.02	0.31	9,508	.97
Days	7.78	3,559	<.0001	3.93	3,572	.009	0.81	9,544	.61
Mania									
Severity	6.40	3,545	<.001	0.28	3,580	.84	2.09	9,539	.03
Days	7.76	3,551	<.0001	0.71	3,554	.55	1.44	9,542	.17
No. of episodes (*DSM IV*)	19.26	3,515	<.0001	4.45	3,587	.004	2.70	9,504	.004
Ultradian cycling days	4.08	3,439	<.007	2.61	3,574	.051	1.51	9,428	.12
Euthymic days	18.58	3,540	<.0001	5.29	3,592	.001	1.04	9,525	.41

[a]Onset group refers to those who began their illness with first episodes in childhood (< 13 years), adolescence (13–18 years), early adulthood (19–29 years), and late adulthood (≥ 30 years).
[b]All outcome measures significantly improved with time in network as assessed in years 1–4 of follow-up.
[c]Those who had an early age at onset of bipolar disorder (in childhood, before age 13) fared more poorly as adults on most outcome measures except for manic severity and duration.
[d]The significant interaction for manic severity and number of episodes indicates that the large age-at-onset group differences that were present in year 1 became much more attenuated in the later years in the network (years 3 and 4); ie, these measures became more typical of the other age-at-onset groups with continued naturalistic treatment in the network.

(n = 181), and fourth (n = 137) years of participation in the network as a function of the 4 groups of patients categorized by age at onset of bipolar disorder. Despite intensive monitoring and treatment,[9] those with early onset continued to show a relatively poor outcome throughout the 4 years on measures such as severity of depression and days euthymic, while the age-at-onset differences in mania and cycling as a function of early versus late onset became progressively less apparent.

For severity of depression, the linear mixed model examining severity of depression showed a main effect for onset group and time, but not for interaction between group and time (Table 1). The earliest onset group had the most severe depression, but the only significant difference after correction for multiple comparisons was with the onset group aged 19–29 years. The first year of follow-up included significantly worse depression than the ensuing 3 years. Results were similar for the number of days depressed. There were significant main effects for group and time, but not for interaction. The childhood-onset group had more days depressed overall than the onset group aged 19–29 years.

For severity of mania, there was a significant main effect of time, but no onset group main effect (Table 1). The childhood-onset and adolescent-onset groups had less severe mania in the fourth year compared to the first. The significant interaction indicated that the early-onset groups became more like those with later onsets as a function of years in the network. With number of days manic, there was only a significant main effect of time. Patients had fewer days manic from the first year to the second and from the second year to the fourth.

For the number of *DSM-IV* episodes observed prospectively, both main effects and the interaction were significant (Table 1). In the first year, the 2 earliest onset groups had more episodes than the 2 later onset groups. The childhood-onset group had more episodes than the adolescent-onset group. In the second year, only the youngest onset group had more episodes than the latest onset group. There were no differences in the third and fourth years. All of the groups had more episodes in the first year than in the fourth year, except the group with onset at age 19–29 years. Examination of the number of days with ultradian cycling revealed only a significant time effect, with all of the onset groups having fewer cycling days in the fourth year than in the first year.

The linear mixed model for days well (euthymic) had significant main effects for time in network and onset group, but not for interaction (Table 1). Patients had fewer days well in the first year compared to other years and fewer days well in year 2 than in the fourth year. The earliest onset group had significantly fewer days well throughout their time in the network than the other groups, but only the differences with the 2 adult-onset groups were significant after correction for multiple comparisons.

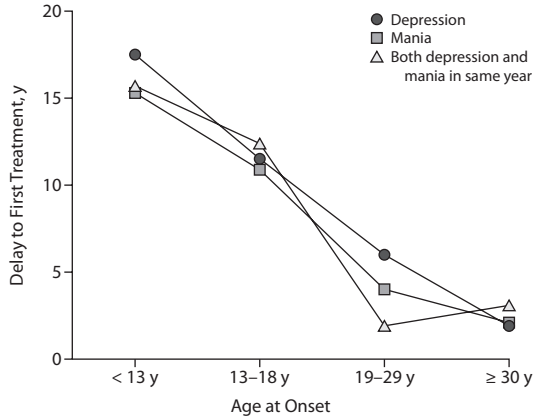
Age at Onset and Delay to First Treatment

A Pearson correlation showed a significant inverse relationship between age at onset and delay to first treatment ($r = -0.46$, $P < .001$), such that patients with earlier onset illness had longer delays to first treatment. One potential confound is the type of mood state (polarity) at the first episode of illness, so additional correlations divided the sample by the polarity of first episode. These correlations were highly significant and of the same magnitude for all groups, whether the first episode was depression ($r = -0.47$, $P < .001$), mania/hypomania ($r = -0.42$, $P < .001$), or depression and mania/hypomania simultaneously ($r = -0.44$, $P < .001$). Further, since the age of the cohort examined could influence the results due to changes in the medications available, correlations were examined for patients entering the research network under age 30, between ages 30 and 39, between ages 40 and 49, and at age 50 or older. All of these correlations were highly significant and of a similar magnitude as well (under age 30: $r = -0.67$, $P < .001$; ages 30–39: $r = -0.68$, $P < .001$; ages 40–49: $r = -0.61$, $P < .001$; age 50 or older: $r = -0.56$, $P < .001$). Thus, the polarity at first episode (Figure 2) and the age cohort did not influence the relationship between age at onset and delay to first treatment.

Contributions of Age at Onset and Delay to First Treatment in Predicting Prospective Outcome in Year 1 of Prospective Follow-Up

First, Pearson correlations were used to examine the relationship between outcome measures and the age at onset

Figure 2. Relationship Between Age at Onset of Bipolar Illness and Years of Delay to First Treatment According to Polarity of First Episode[a]



[a]Delay to first treatment for mania or depression remains inversely correlated to age at onset of illness regardless of the polarity of the first episode, ie, depression with dysfunction, mania (or hypomania), or both episodes occurring in the same year.

Table 2. Treatment Delay Is an Independent Correlate of Poor Prospective Outcome in Adults With Bipolar Disorder[a]

Adult Outcome Measure	Pearson Correlations				Linear Regressions			
	Age at Onset		Treatment Delay		Age at Onset		Treatment Delay	
	r	*P*[b]	*r*	*P*[b]	β	*P*	β	*P*[b]
Depression								
Severity	0.08	.07	−0.15	**.002**	0.02	.69	−0.14	**.01**
Days	−0.08	.08	0.13	**.006**	−0.03	.64	0.12	**.02**
Mania								
Severity	−0.13	**.004**	0.11	**.02**	−0.10	.06	0.07	.22
Days	−0.10	**.03**	0.10	**.04**	−0.07	.21	0.07	.22
Euthymic days	0.17	**<.001**	−0.21	**<.001**	0.09	.11	−0.17	**<.001**
Ultradian cycling days	−0.16	**<.001**	0.17	**<.001**	−0.10	.06	0.12	**.02**
No. of episodes (*DSM-IV*)	−0.22	**<.001**	0.28	**<.001**	−0.12	**.02**	0.22	**<.001**

[a]Both earlier age at onset of bipolar disorder and longer time delay to first treatment for mania or depression correlate significantly with multiple prospective measures in the first-year follow-up of a more adverse outcome in adulthood (left columns). Independently of age at onset, treatment delay is a significant correlate of a poor outcome on all measures except manic severity and duration.
[b]Boldface type indicates statistical significance.

and delay to treatment variables separately. The length of delay to first treatment was correlated with each measure of outcome in the first year of follow-up in an adverse direction (Table 2; left-side columns). The strongest relationships were with the total number of episodes, both measures of depression, days euthymic, and days of ultradian cycling. Only the correlations with severity of mania and days manic would lose significance with a Bonferroni correction.

Correlations with age at onset revealed relationships with a similar magnitude. However, correlations with severity of depression and days depressed were not significant, and the correlation with days manic was not significant after Bonferroni correction. Again, the correlation with number of episodes was the strongest.

Next, multiple linear regressions were run to examine the independent contributions of age at onset and delay to first treatment to outcome in the first year, as this year had the largest N and would be less affected by the type of prospective treatment received in the network. Table 2 (right-side columns) shows the standardized regression coefficients from each regression with a main-effects model. Interactions were not included since that reduced tolerance to unacceptable levels without explaining additional variance. The delay to first treatment was independently related to the duration and severity of depression, days well, days of ultradian cycling, and total number of episodes. Early age at onset was an independent contributor only to the total number of episodes observed prospectively.

DISCUSSION

These data extend previous reports indicating that early age at onset is a poor prognosis factor for outcome retrospectively reported by adult outpatients with bipolar disorder studied in research networks.[2,3] Our previous short report confirmed these self-report findings with prospective clinician ratings for 1 year,[2] and the current study extends many of these findings over 4 years of prospective follow-up. In addition, the new data provided here supplement previous observations in several different ways. As illustrated in Figure 2, the striking inverse relationship between earlier age at onset of illness and longer delay to first treatment occurred whether the first episode was manic, depressive, or both in the same year. As illustrated in Table 2, we found that the duration of the delay to first treatment had an independent relationship to the prospective measures of severity of depression, number of days depressed, number of days euthymic, number of episodes, and days of ultradian cycling. Age at onset had an independent contribution only to the number of episodes observed prospectively. Whether early intervention to shorten the delays to first treatment could alter this adverse course of illness in adulthood, or whether early onset is a harbinger of worse course regardless of intervention, remains to be studied.

Our initial report, examining the first year, found that an early age at onset was a poor prognostic factor for all 7 variables examined: severity and duration of mania and of depression, days euthymic, number of episodes, and days of ultradian cycling. Extending the analysis to cover 4 years found this relationship to still exist for severity and duration of depression and days euthymic. The differences seen in the first year for severity of mania and days euthymic as a function of the childhood-onset group were attenuated and no longer present with additional time and treatment in the network. When we examined all 4 years, there were no longer any significant group differences in days manic or days of ultradian cycling. This finding suggests that the early age-at-onset grouping is associated with a poor prognosis for depressive symptoms in adulthood that even dedicated prospective treatment over 4 years does not fully alleviate.

In contrast, the relatively poorer manic outcomes initially seen in the early-onset group do dissipate over the longer time period in the network with careful prospective assessment and treatment. It is of interest that Kraepelin,[14] Angst,[15] and others have seen a predominance of mania in childhood and then relatively more depression in adulthood, and, here, we saw that early-onset illness and delayed treatment were the most closely associated with measures of depression as adults. This finding might suggest that the depressive predominance in adulthood emerges regardless of initial polarity of episodes or that the depressive phase is relatively more difficult to treat than mania in adults.

The epidemiologic data of Wang and colleagues[16] could not address the issue of whether the strong inverse relationship they observed between early onset and long delays to first treatment was clinically consequential and related to a poor outcome. They noted that some investigators had speculated that these early symptoms might just reflect relatively mild illness that did not require treatment and might not have major clinical consequences over the short term or a lifetime. However, the combined retrospective data of Perlis et al[3] and ours strongly suggest the opposite. That is, early childhood onset and the associated long delays to first treatment are, in fact, associated with serious morbidity, comorbidity, and suicidality throughout the entire course of illness,[2] including that now observed prospectively on several measures of depression persisting over the whole period of 4 years of follow-up in adults who were a mean age of 42 at network entry.

We wished to assess whether the extraordinarily long delays from onset of first symptoms to first treatment for either depression or mania varied according to the mood phase at onset, ie, either depression or hypomania/mania, because this differentiation could relate to a potential artifact. That is, patients with depressive onset might have been presumed to be unipolar, might have experienced multiple depressions prior to their first episode of mania, and, therefore, might not have been treated with antidepressant, antimanic, or mood stabilizing agents for a considerably longer period of time compared with those with mania as the first symptom of bipolar onset. This explanation, which presupposes that mania might be more problematic than depression and trigger earlier treatment, did not appear to account for the generally extreme time lags from first symptoms to first medication (Figure 2), although delays were several years longer in those with depressive onsets in the childhood and young adulthood illness-onset groups. Alternatively, those with initial depressive presentation might have eventually been treated with antidepressants, which could have worsened the course of illness.

We also examined whether the relationship of age at onset and delay to first medication would persist in more recent decades as the diagnosis of bipolar disorder may have become more recognized in children. There is considerable evidence supporting a cohort effect,[17] ie, that each birth cohort since World War I has shown an increased incidence and younger age at onset of both unipolar and bipolar disorder. In this study, we found that the substantial inverse relationship between age at onset and treatment delay persisted in each age cohort grouped by decades. In this study, we found that there was some reduction in the delay to first treatment in the more recent decades.

These data are compatible with the recent epidemiologic data of Wang et al,[16] who also found that the age at onset and delay to first treatment were inversely related in affective disorders (unipolar and bipolar) grouped together. The Wang et al[16] study taken together with the clinical population data here and the results of Perlis et al[3] suggest that early-onset bipolar illness was not only relatively common some 20 or more years ago but also was almost always not recognized or treated with medications in an expeditious fashion.

These data also indirectly address the ongoing debate about the extent of bipolar illness appearing in current childhood- and adolescent-aged youngsters. For example, Moreno et al[18] reported a 40-fold increase in visits for bipolar disorder diagnosis in youngsters over a recent 10-year interval, while visits for adults only doubled. Controversy remains about the precise diagnostic criteria for bipolar disorder in children and about symptom thresholds for these presentations in youngsters, particularly for bipolar II and bipolar not otherwise specified (NOS) subtypes.[19–24] Our data and that of Perlis et al[3] in carefully diagnosed adults indicate that childhood- and adolescent-onset bipolar illness was prevalent (at least in the United States[25]) even several decades ago but was rarely recognized. Whether the marked increase in the diagnosis more recently represents increased recognition, a true increase, or over-diagnosis remains to be ascertained.

Our retrospective data and that of Perlis et al[3] on the adverse course of bipolar illness in those with the earliest onset are also highly consistent with recent clinical samples in children followed longitudinally. Children with bipolar disorder tend to remain ill more than 50% of the time in follow-up and take a mean duration of more than 9 months to stabilize.[22,26–28] The recent 8-year follow-up of bipolar I children who were a mean age of 11 years at intake is particularly telling.[29] These children with an early onset of mania were ill 60% of the weeks of long-term follow-up and showed a continuity of mania (often with ultradian cycling) and occurrence of manic episodes into adulthood in the group that had reached age 18 and beyond. These children had been treated naturalistically in the community, but the intensity of that treatment and the extent to which consensus guidelines about the recommended use of mood stabilizers and atypical antipsychotics[20] were adhered to was not specified.

While age at onset and the duration of time to first treatment are moderately inversely correlated, delay to first treatment was found to have an independent contribution to depression severity and duration, days euthymic, days of ultradian cycling, and number of episodes in 519 of our adult outpatients rated prospectively in the first year in the network. Age at onset as a continuous measure was also related adversely to many prospective illness outcome variables in adults (Table 2, left side) but had an independent

contribution (over that of treatment delay) only to the number of episodes observed prospectively (Table 2, right side).

These data indicating an effect of delay to first treatment on many measures of long-term outcome are noteworthy as quite different from those reported by Baldessarini et al.[30] They found, in a very different setting, examining the onset of long-term lithium prophylaxis (as opposed to first acute pharmacologic treatment of either mood phase in our cohort), that the lag to onset of prophylaxis initiation was not related to a poor response to lithium in adults. They nonetheless recommended judicious, early treatment. Our data based on events that occurred when our adults were children and adolescents are highly supportive of the need for early effective intervention, as both early onset of illness and the length of delay to first treatment are related to a more difficult course of bipolar illness into adulthood.

Our findings are consistent with the general view that, if affective episodes are left untreated for prolonged periods of time and accumulate, this scenario is associated with the increased vulnerability to recurrences[31,32] and the development of treatment resistance, particularly in the depressive domain.[6,33] This situation may have particularly pernicious implications for children, who may be more vulnerable because of their neurobiologic, social, and academic developmental time frames and trajectories.[34]

The clinician-rated follow-up data reported here suggest that the greater severity and duration of depression was not related to differential or poor treatment during follow-up as adults. All patients were engaged in naturalistic treatment and follow-up in academic institutions known for expertise in the treatment of bipolar disorder. The patients were treated with substantial numbers of mood stabilizers, antidepressants, antipsychotics, benzodiazepines, and other categories of agents in an effort to bring their symptomatology under control.[9,33,35] Despite this treatment, those with early-onset illness remained most treatment-resistant by multiple measures. It could still be argued, however, that the associated long delays to first treatment in the community combined with the possibility of less than ideal treatment once it did begin (such as the use of antidepressant monotherapy for those adults with a new diagnosis of bipolar disorder, as pointed out by Baldessarini et al[36]) could combine to result in the occurrence of greater numbers of previous episodes, which themselves[31,32,37] were contributing to the poor prospective outcomes compared to those with onset of illness in adulthood.

Limitations

There are a number of limitations to the data reported here. One might challenge the reliability and validity of the stated time of illness onset or age at first treatment based on self-report and retrospective recall. However, we observed a high correlation ($r = 0.80$) between self-reported age at onset and that acquired by a formal SCID interview. Since age at onset of depression was queried as it related to symptoms associated with functional impairment, such retrospectively generated estimates would be likely to meet *DSM-IV* criteria, especially since depression of a few days' duration (as opposed to several weeks) is unlikely to be remembered several decades later. Similarly, it would be hard to imagine that adults with clear-cut experiences of hypomanic or manic episodes would remember manic or hypomanic symptoms that were trivial and did not meet *DSM-IV* criteria. Thus, these ages at onset are likely to represent a conservative estimate of the real age at onset that would be identified prospectively at a time closer to symptom onset and observed prospectively. Moreover, our data closely match those of Perlis et al[3] for distribution of ages at onset, as well as those obtained in some other countries, in part prospectively.[38,39]

In addition, as illustrated in Table 1 and in Figure 1, those with the self-reported and SCID-diagnosed early age at onset not only had the most adverse outcomes in the first year of prospective follow-up, but also, in terms of the severity of their depression and days euthymic per year, these adults never caught up with their counterparts who had had later onset of bipolar illness. This continued high rate of poor response to treatment in years 2 to 4 of follow-up could be viewed as being artificially driven by a self-selection factor by which those with the most difficult illnesses may have been the ones who stayed in the network the longest. However, when we reexamined the year 1 to year 4 data including only those who remained in the network in year 4, the findings remained similar: those with early onset of illness fared more poorly.

CONCLUSIONS AND IMPLICATIONS

Therefore, both retrospective report of illness course with treatment in the community[2,3] and prospective assessments during treatment by experts over a period of 1 to 4 years (this article) all converge toward the conclusion that early-onset bipolar disorder (as it was previously poorly recognized and treated only after many years of illness) had an extended poor prognosis over a patient's entire lifetime. These data are also convergent with the recent prospective follow-up studies of children with bipolar illness in the community[26,27,29] and in clinic settings,[22,28] which indicate that childhood-onset illness is difficult to treat and achieve initial stabilization and is associated with a high relapse rate. With the increasing recognition of childhood bipolar illness in both clinical treatment[18] and controlled-trial settings,[40,41] it is likely that the long delays to first treatment that were apparent from our study a generation ago may, in fact, be becoming attenuated. This is suggested by the observation that the treatment delays in the more recent birth cohorts (arranged by age at network entry) are somewhat shorter than in the older individuals.

Given the large number of patients involved (50%–66% of adults with bipolar illness studied in academic treatment networks report their onset of bipolar illness to be in childhood or adolescence[2,3]) and the gravity of the sustained adverse outcome as adults, these data speak to the importance of attempting to modify this long-term poor outcome with earlier and more effective treatment of children and adolescents with bipolar symptoms meeting *DSM-IV* criteria for bipolar

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disorder. Whether or not earlier and more concerted treatment will in fact ameliorate the poor long-term prognosis remains for more definitive assessment and future study. However, the finding reported here that the delay to first treatment has an independent contribution to many measures of poor outcome in adults many years later (at a mean age of 42) suggests the possibility that early intervention in childhood-onset bipolar illness could very well yield a more positive ultimate illness course.

The Geller et al[29] data do much to quench the controversies about the continuity of bipolar I illness from childhood to adulthood, but treatment-related studies continue to be relatively lacking for these children and are largely absent for the large proportion of children with a bipolar disorder NOS diagnosis, 25% of whom convert to bipolar II or bipolar I disorder after several years of follow-up.[22,42]

Given the seriousness of bipolar disorder in children in the short and long term, the establishment of temporary working diagnostic guidelines and common terminology by expert consensus could help to expedite treatment studies.[43] Now that we know that childhood-onset bipolar illness (and its associated long lags to first treatment) is linked to a difficult course of illness in the short term,[22,26–28] intermediate term,[29] and long term (references 2 and 3 and this study), new treatment initiatives for these children are needed. Defining the most effective range of psychosocial and pharmacologic interventions for this group of children deserves a high priority for study.

Drug name: lithium (Lithobid and others).
Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no medications for the treatment of bipolar disorder are approved by the US Food and Drug Administration for children under 10 years old.
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Financial disclosure: **Dr Post** has been a consultant to, has received honoraria from, and has been a member of the speakers or advisory boards for Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, and Pfizer. **Dr Kupka** has received research grants from AstraZeneca and honoraria from Eli Lilly, Janssen-Cilag, Bristol-Myers Squibb, and AstraZeneca. **Dr Keck** is a principal or coinvestigator on research studies sponsored by Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Janssen, the National Institute of Mental Health, the National Institute of Drug Abuse, Pfizer, and UCB Pharma and has been reimbursed for consulting to, in the past 2 years, Bristol-Myers Squibb, Eli Lilly, Forest, Organon, and Pfizer. Dr Keck is also inventor on US Patent No. 6,387,956: Shapira NA, Goldsmith TD, Keck PE Jr (University of Cincinnati), Methods of Treating Obsessive-Compulsive Spectrum Disorder Comprises the Step of Administering an Effective Amount of Tramadol to an Individual; filed March 25, 1999; approved May 14, 2002. **Dr McElroy** is a consultant to or member of the scientific advisory boards of Eli Lilly and Schering-Plough and is a principal or coinvestigator on research studies sponsored by Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Jazz, the Marriott Foundation, the National Institute of Mental Health, Orexigen, Shire, and Takeda. Dr McElroy is also inventor on US Patent No. 6,323,236, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and, along with the patent's assignee, the University of Cincinnati, has received payments from Johnson & Johnson Pharmaceutical Research & Development, which has exclusive rights under the patent. **Dr Altshuler** serves on the advisory boards of Forest and Sepracor. **Dr Frye** has received grant support from Pfizer (drug supply: varenicline); has been a consultant to Cephalon, Dainippon Sumitomo, Ortho McNeil/Janssen, Johnson & Johnson, Schering-Plough, and Pfizer; and has participated in supported CME activities for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Otsuka, Pfizer, and Schering-Plough. **Dr Rowe** is a consultant for Mid-Atlantic Kaiser Permanente. Dr Rowe's spouse/partner is an employee of Mid-Atlantic Kaiser Permanente. **Dr Grunze** has received grant/research support, consulting fees, and honoraria within the last 3 years from AstraZeneca, Bial, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Organon, Pfizer, Sanofi-Aventis, Servier, United BioSource Corporation, and UCB Belgium. **Dr Suppes** has received grant support or clinical study medications from AstraZeneca, the National Institute of Mental Health, and Pfizer; has received honoraria from Wolters Kluwer, Pharma Solutions (CNS Drug Supplement); and receives royalties from Jones and Bartlett (formerly Compact Clinicals). **Dr Nolen** has received grants from The Netherlands Organization for Health Research and Development, the European Union, The Stanley Medical Research Institute, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Wyeth; has received honoraria or speaker's fees from AstraZeneca, Eli Lilly, Pfizer, Servier, and Wyeth; and has served on the advisory boards of AstraZeneca, Cyberonics, Pfizer, and Servier. **Ms Leverich** and **Mr Luckenbaugh** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.
Funding/support: Original data collection was supported by The Stanley Medical Research Institute, Chevy Chase, Maryland. Data analysis was supported by the National Institute of Mental Health, Bethesda, Maryland, and a private foundation.

REFERENCES

1. Leverich GS, Post RM. Course of bipolar illness after history of childhood trauma. *Lancet*. 2006;367(9516):1040–1042.
2. Leverich GS, Post RM, Keck PE Jr, et al. The poor prognosis of childhood-onset bipolar disorder. *J Pediatr*. 2007;150(5):485–490.
3. Perlis RH, Miyahara S, Marangell LB, et al. STEP-BD Investigators. 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). *Biol Psychiatry*. 2004;55(9):875–881.
4. Perkins DO, Gu H, Boteva K, et al. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry*. 2005;162(10):1785–1804.
5. Post RM, Nolen WA, Kupka RW, et al. The Stanley Foundation Bipolar Network, I: rationale and methods. *Br J Psychiatry*. 2001;178(suppl): s169–s176.
6. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH-Life Chart Method. *J Clin Psychiatry*. 2003;64(6):680–690; quiz 738–739.
7. Leverich GS, McElroy SL, Suppes T, et al. Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol Psychiatry*. 2002; 51(4):288–297.
8. Leverich GS, Altshuler LL, Frye MA, et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J Clin Psychiatry*. 2003;64(5):506–515.
9. Kupka RW, Luckenbaugh DA, Post RM, et al. Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. *Am J Psychiatry*. 2005;162(7): 1273–1280.
10. Keck PE Jr, Mintz J, McElroy SL, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry*. 2006;60(9):1020–1022.

11. Leverich GS, Post RM. Life charting of affective disorders. *CNS Spectr*. 1998;3(5):21–37.
12. Denicoff KD, Leverich GS, Nolen WA, et al. Validation of the prospective NIMH-Life-Chart Method (NIMH-LCM-p) for longitudinal assessment of bipolar illness. *Psychol Med*. 2000;30(6):1391–1397.
13. Denicoff KD, Ali SO, Sollinger AB, et al. Utility of the daily prospective National Institute of Mental Health Life-Chart Method (NIMH-LCM-p) ratings in clinical trials of bipolar disorder. *Depress Anxiety*. 2002;15(1): 1–9.
14. Kraepelin E. Robertson GM, ed, Barclay RM, trans. *Manic-Depressive Insanity and Paranoia*. Edinburgh, Scotland: Livingstone; 1921.
15. Angst J. Bipolar disorder—methodological problems and future perspectives. *Dialogues Clin Neurosci*. 2008;10(2):129–139.
16. Wang PS, Berglund P, Olfson M, et al. Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):603–613.
17. Lange KJ, McInnis MG. Studies of anticipation in bipolar affective disorder. *CNS Spectr*. 2002;7(3):196–202.
18. Moreno C, Laje G, Blanco C, et al. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry*. 2007;64(9):1032–1039.
19. Carlson GA. Early onset bipolar disorder: clinical and research considerations. *J Clin Child Adolesc Psychol*. 2005;34(2):333–343.
20. Kowatch RA, Fristad M, Birmaher B, et al. Child Psychiatric Workgroup on Bipolar Disorder. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2005;44(3): 213–235.
21. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry*. 2005;44(9): 846–871.
22. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*. 2006;63(2):175–183.
23. Biederman J, Klein RG, Pine DS, et al. Resolved: mania is mistaken for ADHD in prepubertal children. *J Am Acad Child Adolesc Psychiatry*. 1998;37(10):1091–1096, discussion 1096–1099.
24. Reichart CG, Nolen WA. [Diagnosis and treatment of bipolar disorder in children]. (Article in Dutch) *Ned Tijdschr Geneeskd*. 2007;151(11): 630–634.
25. Post RM, Luckenbaugh DA, Leverich GS, et al. Incidence of childhood-onset bipolar illness in the USA and Europe. *Br J Psychiatry*. 2008;192(2): 150–151.
26. Geller B, Craney JL, Bolhofner K, et al. Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry*. 2002;159(6):927–933.
27. Geller B, Tillman R, Craney JL, et al. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. *Arch Gen Psychiatry*. 2004;61(5): 459–467.
28. DelBello MP, Hanseman D, Adler CM, et al. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. *Am J Psychiatry*. 2007;164(4):582–590.
29. Geller B, Tillman R, Bolhofner K, et al. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. *Arch Gen Psychiatry*. 2008;65(10):1125–1133.
30. Baldessarini RJ, Tondo L, Baethge CJ, et al. Effects of treatment latency on response to maintenance treatment in manic-depressive disorders. *Bipolar Disord*. 2007;9(4):386–393.
31. Kessing LV, Andersen PK, Mortensen PB. Predictors of recurrence in affective disorder. A case register study. *J Affect Disord*. 1998;49(2): 101–108.
32. Post RM. Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neurosci Biobehav Rev*. 2007;31(6):858–873.
33. Nolen WA, Luckenbaugh DA, Altshuler LL, et al. Correlates of 1-year prospective outcome in bipolar disorder: results from the Stanley Foundation Bipolar Network. *Am J Psychiatry*. 2004;161(8):1447–1454.
34. Post RM, Miklowitz D. The role of stress in the onset, course, and progression of bipolar illness and its comorbidities: implications for therapeutics. In: Miklowitz DJ, Cicchetti D, eds. *Understanding Bipolar Disorder: A Developmental Psychopathology Perspective*. New York, NY: Guilford Press; 2010.
35. Post RM, Leverich GS, Nolen WA, et al. Stanley Foundation Bipolar Network. A re-evaluation of the role of antidepressants in the treatment of bipolar depression: data from the Stanley Foundation Bipolar Network. *Bipolar Disord*. 2003;5(6):396–406.
36. Baldessarini R, Henk H, Sklar A, et al. Psychotropic medications for patients with bipolar disorder in the United States: polytherapy and adherence. *Psychiatr Serv*. 2008;59(10):1175–1183.
37. Post RM. Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. *J Psychiatr Res*. 2007;41(12):979–990.
38. Soutullo CA, Chang KD, Díez-Suárez A, et al. Bipolar disorder in children and adolescents: international perspective on epidemiology and phenomenology. *Bipolar Disord*. 2005;7(6):497–506.
39. Diler RS, Uguz S, Seydaoglu G, et al. Mania profile in a community sample of prepubertal children in Turkey. *Bipolar Disord*. 2008;10(4): 546–553.
40. Findling RL, McNamara NK, Youngstrom EA, et al. Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2005; 44(5):409–417.
41. Findling RL, McNamara NK. Atypical antipsychotics in the treatment of children and adolescents: clinical applications. *J Clin Psychiatry*. 2004; 65(suppl 6):30–44.
42. Leibenluft E. Pediatric bipolar disorder comes of age. *Arch Gen Psychiatry*. 2008;65(10):1122–1124.
43. Post RM, Kowatch RA. The health care crisis of childhood-onset bipolar illness: some recommendations for its amelioration. *J Clin Psychiatry*. 2006;67(1):115–125.

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