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Age of Onset and the Prospectively Observed Course of Illness in Bipolar Disorder

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Abstract

Background—To test the validity of age-of-onset grouping in bipolar disorder through the use of prospectively observed time in mood episodes.

Methods—Age-of-onset ranges from prior admixture analyses were used to divide 427 individuals with bipolar I or bipolar II disorder into early-, middle- and late- onset groups. These were compared by the proportions of weeks depressed and manic or hypomanic during a mean (SD) prospective follow-up of 17.4 (8.4) years.

Results—As predicted, the group with the earliest onsets reported at intake more previous episodes, more suicide attempts and panic attacks. An early age of onset, but not current age, was predictive of significantly more time in depressive episodes during follow-up but was not predictive of time in manic or hypomanic episodes.

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Conflict of Interest
Dr. Martin Keller discloses that he is a consultant for CENEREX, Medtronic, and Sierra Neurophamaceuticals, does grant research for Pfizer and is on the advisory board for CENEREX. The other authors report no conflicts.

Contributors
Drs. Coryell, Endicott, and Keller participated in the original design of the CDS, in the acquisition of NIMH support, and in the collection and analysis of data. Drs. Fiedorowicz and Leon have been active in the analysis of data and preparation of manuscripts.

Limitations—This was a naturalistic study with no control of treatment so variability in treatment may have obscured relationships between predictors and outcomes. Age of onset was retrospectively determined and subject to inaccuracies in recall.

Conclusions—An early age of onset conveys, to a modest degree, a poorer prognosis as expressed in more depressive morbidity.

Keywords

bipolar disorder; age-of-onset; follow-up; prognosis

Introduction

Efforts to identify genetic factors in susceptibility to bipolar disorders have struggled with the problem of phenotypic heterogeneity. Although no clear solution has emerged, grouping by age-of-onset has been the approach most commonly taken. Much of the empirical support for this has come from concordant results across a series of admixture analyses. Of seven that examined the age-of-onset distributions of bipolar cohorts, six (Bellivier et al., 2001; Bellivier et al., 2003; Hamshere et al., 2009; Lin et al., 2006; Manchia et al., 2008; Tozzi et al., 2011) determined that they resolved into three groups and one (Kennedy et al., 2005b) found evidence for two groups. Among those that found the best solution in three onset groups, mean ages for the earliest-onset category ranged from 16.1 years (Tozzi et al., 2011) to 18.7 years (Hamshere et al., 2009). Lowest and highest mean ages-of-onset for the middle groups were 24.3 years (Manchia et al., 2008) to 28.3 years (Hamshere et al., 2009), respectively, and the mean ages for the oldest onset group ranged from 32.2 (Tozzi et al., 2011) to 46.2 (Bellivier et al., 2001).

Most efforts to demonstrate the clinical validity of age-of-onset groups in bipolar disorder have retrospectively compared the youngest onset group with all later-onset individuals. These comparisons have shown the early-onset group to have a greater likelihood of prior suicide attempts (Bellivier et al., 2001; Carter et al., 2003; Lin et al., 2006; Manchia et al., 2008; Perlis et al., 2004; Tozzi et al., 2011), and to have higher rates among family members of psychiatric disorders (Bellivier et al., 2001), affective disorders (Hamshere et al., 2009), or bipolar disorders (Kennedy et al., 2005a; Schurhoff et al., 2000). Most of the other efforts retrospectively assessed clinical features that have distinguished early-onset groups have indicated that early-onset individuals have a poorer prognosis. Accordingly, early-onset bipolar disorder has been associated with more past episodes (Hamshere et al., 2009; Lin et al., 2006; Perlis et al., 2004), a higher likelihood of rapid cycling (Carter et al., 2003; Hamshere et al., 2009; Lin et al., 2006) and of psychotic features (Bellivier et al., 2001; Kennedy et al., 2005b; Schurhoff et al., 2000), and higher rates of co-morbidity with anxiety (Carter et al., 2003; Schurhoff et al., 2000) or substance abuse disorders (Kennedy et al., 2005a; Lin et al., 2006; Perlis et al., 2004).

Demonstrations that early-onset bipolar disorder differs prognostically from later-onset groups are viewed as evidence that heterogeneity is meaningfully reduced by using age of onset to sub-classify bipolar disorder. Yet, conclusions that early-onset illness differs prognostically from later-onset bipolar illness so far rests, with few exceptions (Carlson et al., 2002) on retrospective assessments of course variables. Such studies are likely to be confounded by recall deficiencies that operate differentially across age-of-onset groupings, because older individuals a first episode that may be decades past than are longer individuals who initial episodes are much more recent. Moreover, existing reports have not considered the effects of current age on course variables. Older-onset individuals cannot be young at the time of assessment, but early-onset individuals can and youth, itself, may shape phenomenology and course in important ways. The following report aims to use the results

of a long-term, high-intensity follow-up of a carefully described cohort to determine whether important differences in course of illness exist between age-of-onset groupings derived from an aggregate of previous admixture results.

Methods

Subjects

Between 1978 and 1981, inclusive, the National Institute of Mental Health Collaborative Depression Study (CDS) recruited inpatients and outpatients as they sought treatment for mania, major depression, or schizoaffective disorder at any of five medical centers: Massachusetts General Hospital in Boston; New York State Psychiatric Institute and Columbia Presbyterian Hospital in New York City; Rush Presbyterian Hospital in Chicago; Washington University in St. Louis; and the University of Iowa Hospitals & Clinics in Iowa City. All met Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) for one of the requisite diagnoses and were 18 years or older, English speaking and Caucasian. All participants provided informed consent and recruitment did not influence treatment received. Treatment selection was therefore naturalistic throughout followup.

In the following analysis, subjects designated as having bipolar I or bipolar II disorder had current or past episodes of mania, hypomania, or schizoaffective mania at the time of the baseline evaluation or experienced either syndrome during follow-up. The RDC definition of the mainly-affective subtype of schizoaffective disorder is equivalent to DSM-IV criteria for bipolar or major depressive disorder with mood-incongruent psychotic features. Subjects with the mainly-affective subtype of schizoaffective disorder diagnosis were therefore included in the present analysis. Subjects with less than six months of follow-up were excluded, leaving 427 subjects for analysis.

The average of the means and the average of the standard deviations of the ages of onset described in the 6 previously mentioned admixture analyses were used to set the limits of the three age-of-onset groups. Because the mean age of onset across the 6 early-onset groups was 17 years and the mean standard deviation was 3.4, individuals with ages of onset of 20 or less comprised the youngest onset group. Because the means of the means and SDs of the oldest groups were 38.9 years and 9.5 years, respectively, the lower age limit of the oldest group was 30.

Procedures

Carefully trained professional raters administered the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978) as the core diagnostic instrument. The SADS individually characterized a wide scope of symptoms with explicitly anchored, six-point severity ratings. It also included items that assessed the healthiest levels of social functioning and of overall functioning for the preceding five years. The numbers of previous suicide attempts were ascertained as well as the intent and potential lethality of the attempt that was considered to be the most severe. The Research Diagnostic Criteria summary sheet listed the ages of onset for all current and past disorders as the age at which full criteria for the corresponding disorder were first met.

Follow-up assessments took place semi-annually for the first five years after intake and annually thereafter. The mean (SD) length of follow-up was 17.4 (8.3) years and 184 (42.9%) were followed for at least 25 years. The Longitudinal Interval Follow-up Evaluation (LIFE) (Keller et al., 1987) and subsequent, briefer iterations – the LIFE II and Streamlined Longitudinal Interval Continuation Evaluation (SLICE)- used information from subject interview and medical record review to track all RCD disorders active at intake or at any time during follow-up. Interviewers guided subjects to identify points in the follow-up

interval in which symptoms had changed significantly and then directed them to quantify symptoms levels present between those change points.

Psychiatric Symptom Ratings (PSR) for the major mood syndromes of major depression, mania, schizoaffective depression or schizoaffective mania ranged from '1' to '6' with '1' indicating no symptoms, '2' the presence of one or two symptoms to a mild degree, '3' and '4' the continued presence of any episode with less than the number of symptoms necessary for an initial diagnosis, '5' a full syndrome, and 6 a relatively severe full syndrome. Hypomania, minor depression, and intermittent depressive disorder symptoms were rated on three-point scales in which '3' indicated a full syndrome. For the following analyses, any week with a PSR of '3' or more for major, intermittent or schizoaffective depressive disorder indicated the current presence of a depressive episode. Likewise, a manic episode was considered present for all weeks with a PSR of '3' or more for hypomania, mania, or schizoaffective mania.

Data Analysis

The central hypothesis tested was that mood disorder morbidity, quantified as the proportion of weeks during follow-up in episodes either of any depressive disorder, or of any manic/hypomanic disorder, would differ across the three age-of-onset groups such that morbidity would be greatest in the youngest group. Pending support for this omnibus hypothesis, we planned to then conduct pair-wise comparisons between the youngest onset group and the two older onset groups combined. Analyses used multiple linear regression analysis (GLM) (SPSS version 19) applied to bipolar I and bipolar II groups combined with the independent variables of age-of-onset, as predictors and the log-transformed proportion of weeks in depressive or in manic/hypomanic episodes as the outcome variable. Analyses used a logit transformation of the dependent variables because the distributions of both weeks in depressive episodes and weeks in manic/hypomanic episodes were right-skewed. The regression coefficients (3) quantify the magnitude and direction of the association between each predictor and the long-transformed proportion of weeks in depressive or in manic episodes.

Secondary hypothesis testing was undertaken to replicate previously described findings that baseline clinical and historical measures indicative of poor prognosis characterize early-onset groups. Specifically, we expected the earliest onset group, in comparison to the middle and oldest groups, to have higher likelihoods of previous episodes and of rapid cycling, and greater proportions with psychotic features and with co-existing anxiety and substance abuse disorders. Comparisons using categorical measures and those using continuous measures were conducted with chi-square and analysis of variance (ANOVA) procedures, respectively. Group comparisons of time in mood episodes use the non-parametric Kruskal-Wallis test because distributions were skewed.

Results

Prospectively Observed Morbidity

As expected, age-of-onset groups differed significantly by current age and marital status (Table 1). Those in the youngest group were also least likely to be inpatients when recruited but age-of-onset groups did not differ by proportions with bipolar I disorder or by sex. Three-way comparisons of mean and median numbers of weeks in depressive episode differ significantly from the early-onset group having the highest values (Table 2). The median proportion of weeks in depressive episodes experienced by the earlier onset group was 39% higher than the value for the middle onset group and 32% higher than that for the late onset group.

With the logit-transformed proportion of time in depressive episodes as the dependent variable in a linear regression model, and with current age and age-of-onset (youngest vs older) as predictors, age-of-onset (β = −.62, CI = −1.2 to −.03, χ^2 = 4.2, p = .040) was significantly associated with the prospectively observed depressive morbidity but current age was not (β = .000, CI = −.02 to .02, χ^2 = .00, p = .987). Early age of onset remained a significant predictor of depressive morbidity after the distinction between bipolar I and bipolar II was added to the model (β = −.626, CI = −1.2 to −.05, χ^2 = 4.5, p = .033). Neither age nor age-of-onset predicted time in manic or hypomanic episodes.

To provide prospective age-of-onset findings several baseline measures that have previously been shown to predict long-term depressive morbidity in bipolar disorder were added to the GLM models. Bipolar I patients who entered the study in a purely manic episode experienced far less depressive morbidity during follow-up than did those who entered in a depressed or cycling episode (β = 3.1, CI = 2.5 to 3.7, χ^2 = 101.8, p < .0001) while early age only approached significance in this model (β = −.50, CI = −1.0 to .3, χ^2 = 3.4, p = .064). When a previously described composite anxiety symptom score (17) was added to age and early age-of-onset for all bipolar subjects who had had depression during the index episode, it too was much more robustly predictive of depressive morbidity during follow-up and in the opposite direction (β = .124, CI = .065 to .184, χ^2 = 16.7, p < .0001) then was early age of onset (β = −.79, CI = −1.5 to −.05, χ^2 = 4.4, p = 0.036).

Retrospectively Observed Morbidity

Drug use disorder was more likely in the early-onset groups but proportions with other lifetime diagnoses did not differ (Table 3). Panic attacks but not psychotic features were more likely in early onset individuals. Age-of-onset groups did not differ by measures of previous functioning or by illness-related impairment though the early onset group had had twice as many previous episodes (Table 4). The early-onset group reported more previous depressive and manic episodes and was more likely to have made suicide attempts, both during and prior to the index episode.

Discussion

Individuals in the earliest onset group spent 20% more weeks in depressive episodes than did those in either of the other two groups and a simple three-way comparison of mean proportions of follow-up weeks in depressive episodes revealed a significant difference across the three groups. The relationship was clearly stronger for bipolar I subjects than for those with bipolar II disorder.

GLM analyses revealed that the earliest age-of-onset group experienced more depressive morbidity at a modest level of significance after control for current age. Moreover, the phase structure of the index episode (manic only vs other) and anxiety symptom severity among patients whose index episode had included a depressive phase were both much more robustly predictive of future depressive morbidity when tested in the same GLM models.

Many of the baseline descriptors that, in earlier reports, portrayed early-onset individuals as having a poorer prognosis did not do so in the current analysis. Specifically, though the early-onset group was more likely to report current panic attacks they were not more likely to have RDC anxiety disorders, alcoholism, psychotic features, or cycling in the index episode. The best levels of social or overall psychosocial functioning resembled those of older-onset subjects, as did the quality of adolescent friendship patterns. The early-onset group was more likely to have a drug use disorder but, even in this group, the diagnosis was present in only 13%. Earlier onset was, however, clearly associated with histories of recurrence both of depressive and of manic/hypomanic episodes.

The chief strength of these data lay in the duration and surveillance intensity of the follow-up that produced them. An individual with 17 years of follow-up would have undergone a series of 34 interviews after a thorough baseline assessment. The resulting appraisal of prognosis was thus much more trustworthy than a retrospective count of numbers of past episode because such estimates often require recollection spanning many years.

A fundamental caveat, applicable to all long-term follow-up studies, is that treatment for mood disorders varied across individuals at any given point, and over time within individuals. Though nearly all participants were receiving some level of somatotherapy when first assessed (Keller et al., 1982), many later discontinued treatment and many experienced new episodes without seeking treatment (Keller et al., 1986). The current analysis is therefore silent on questions of whether age-of-onset might be associated with poor mood stabilizer or antidepressant response and variability in treatment status may have obscured the prognostic effects of onset age. It should be noted in this context, though, that despite the noise introduced by treatment variability, other baseline features have emerged as powerful predictors of both time in depressive episodes and time in manic or hypomanic episodes (Coryell et al., 2009). In particular, we used a statistical approach very similar to that used here in a recent analysis to assess the prognostic significance of baseline anxiety symptoms. That analysis revealed a robust association between baseline symptoms and subsequent time in depressive episodes that showed little diminution over more than 20 years of follow-up (Coryell et al., 2011). Thus, prognostically important baseline measures can clearly reveal themselves in these data. Early age of onset did so as well but to only a modest degree.

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Table 1

Baseline Measures

	age-of-onset range		
	≤ 20	21–29	≥ 30
n (%)	177 (41.4)	149 (34.9)	101 (23.6)
-female, # (%)	100 (56.5)	87 (58.4)	61 (60.4)
-age, mean (SD)[1]	30.7 (11.3)	34.3 (10.4)	48.9 (11.5)
-marital status, n (%)			
-single	97 (54.8)	54 (36.2)	11 (10.9)
-married	48 (27.1)	59 (39.6)	52 (51.5)
-divorced/separated	31 (17.5)	35 (23.5)	30 (29.7)
-widowed	1 (0.6)	1 (0.7)	8 (7.9)
-inpatient, n (%)[2]	137 (77.4)	125 (83.9)	91 (90.1)
-bipolar I, n (%)	117 (66.1)	93 (62.4)	74 (73.3)
-length of follow-up, years mean (SD)	17.5 (8.4)	18.0 (8.4)	17.5 (8.4)

[1] $F = 90.9$, df = 2/424, $p < .0001$

[2] $\chi^2 = 7.5$, df = 2, $p = 0.024$

Table 2

Weeks in Mood Episodes by Age of Onset Group

	early	middle	late
(%)_of weeks			
-in depressive episodes			
mean (SD)[1]	39.9 (32.3)	31.6 (30.0)	35.1 (31.3)[1]
median	34.6	21.1	23.4[2]
-in manic/hypomanic episode			
mean (SD)	10.0 (16.6)	9.9 (19.0)	7.2 (13.5)
median	1.9	2.5	2.0

[1] p = .038, Krushal-Wallis test

[2] p = .015, Krushal-Wallis test

Table 3

Other Diagnoses, Psychotic Features and Anxiety

	age-of-onset range	
	≤ 20	≥ 21
	n = 177	n = 250
index episode cycling or mixed, n (%)	71 (40.1)	96 (38.4)
total anxiety symptoms score, mean (SD)	19.1 (6.4)	17.9 (6.4)
panic attacks, n (%) [1]	56 (31.6)	51 (20.4)
psychotic features		
-any delusion, n (%)	67 (37.9)	99 (39.6)
-any hallucination, n %	33 (18.6)	39 (15.6)
lifetime diagnoses, n (%)		
-panic disorder	9 (5.1)	8 (3.2)
-obsessive/compulsive	6 (3.4)	5 (2.0)
-phobic disorder	9 (5.1)	14 (5.6)
-GAD	8 (4.5)	12 (4.8)
-any anxiety disorder	28 (15.8)	28 (11.2)
-alcoholism	52 (29.4)	64 (25.6)
-drug use disorder[2]	23 (13.0)	17 (6.8)

[1] $\chi^2 = 7.0$, df = 1, p = .008.

[2] $\chi^2 = 4.9$, df = 1, p = .030

Table 4

Past History

	≤ 20 n = 177	≥ 21 n = 250
past major depressive episodes:		
-number (%) with any[1]	158 (89.3)	174 (69.6)
-total number, median[2]	3	1.5
past manic episodes:		
-number (%) with any [3]	74 (41.8)	75 (30.0)
-total number, median[4]	0	0
suicide attempt, number (%) with any		
-in index episode [5]	51 (28.8)	39 (15.6)
-previous to index episode [6]	80 (45.2)	85 (34.0)
function in previous 5 years, mean (SD):		
-best social functioning	2.8 (1.1)	2.9 (1.1)
-best overall functioning	2.6 (1.1)	2.4 (1.1)
-degree of work impairment	3.0 (2.2)	3.1 (2.3)
adolescent friendship patterns:		
-means (SD)	3.0 (1.2)	2.9 (1.1)

[1] $\chi^2 = 23.2$, df = 1, $p < .0001$

[2] Mann-Whitney U, $p < 0.0001$

[3] $\chi^2 = 6.4$, df = 1. $p = 0.012$

[4] Mann-Whitney U, $p < 0.010$

[5] $\chi^2 = 10.9$, df = 1, $p = .001$

[6] $\chi^2 = 5.5$, df = 1, $p = 0.13$