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Age Transitions in the Course of Bipolar I Disorder

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Abstract

Background—This analysis aimed to show whether symptoms of either pole change in their persistence as individuals move through two decades, whether such changes differ by age-grouping, and whether age of onset plays an independent role in symptom persistence.

Methods—Participants in the NIMH Collaborative Depression Study who completed at least twenty years of follow-up and who met study criteria for bipolar I or schizoaffective manic disorder, before intake or during follow-up, were divided by age at intake into youngest (18–29 years, $n = 56$), middle (30–44 years, $n = 68$) and oldest (greater than 44 years, $n = 24$) groups.

Results—The persistence of depressive symptoms increased significantly in the two younger groups. Earlier ages of onset were associated with higher depressive morbidity throughout the twenty years of follow-up but did not predict changes in symptom persistence. The proportions of weeks spent in episodes of either pole correlated across follow-up periods in all age groupings, though correlations were stronger for depressive symptoms and for shorter intervals.

Conclusions—Regardless of age at onset, the passage of decades in bipolar illness appears to bring an increase in the predominance of depressive symptoms in individuals in their third, fourth and fifth decades and an earlier age of onset portends a persistently greater depressive symptom burden. The degree to which either depression or manic/hypomanic symptoms persist has significant stability over lengthy periods and appears to reflect traits that manifest early in individual's illness.

Keywords

major depression; age periods; age of onset; symptom persistence

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Introduction

Little is known concerning the effects of aging on the manifestations of bipolar disorder. Episodes typically accumulate with the passage of years and studies that were partly or wholly retrospective in their assessments have described decreases in inter-episode durations across successive episodes (Angst J *et al.*, 1973; Kukopulos A *et al.*, 1980; Zis AP *et al.*, 1980; Roy-Byrne Pet *al.*, 1985). Prospective studies, though, have found little evidence of this (Turvey CL *et al.*, 1999; Angst J *et al.*, 2003), suggesting that the apparent increases in episode frequency described in previous studies may have reflected the poorer recall of earlier episodes.

The symptoms of bipolar illness may also undergo qualitative changes with age. Either pole may grow more prominent, and such changes, if they occur, may differ in men and women. Moreover, studies have not as yet addressed the effects of age on overall symptom burden, the product of episode duration and frequency.

Nearly all efforts to study the possible effects of aging on bipolar disorders have compared cohorts grouped by current age. This, however, confounds age-of-onset effects with those of an individual's current age and many reports have associated earlier age at onset with poorer outcomes (Carlson G A *et al.*, 2000; Tohen M *et al.*, 2000; McElroy SL *et al.*, 2001; Carlson GA *et al.*, 2002; Carter TD *et al.*, 2003; Ernst CL *et al.*, 2004). Efforts to statistically control for age-of-onset effects are necessarily limited by the fact that youthful subjects with the illness have only early ages-of-onset.

Circumvention of this problem requires within -subject comparisons across age periods, and this, of course, requires a long period of observation. Frequent follow-up assessments are also necessary because bipolar disorder is typically episodic and widely-spaced assessments are unlikely to adequately capture symptom evolution over time. Finally, transitions across several age periods should be examined to determine whether any observed changes in course apply only to a particular age period.

The NIMH Collaborative Program on the Psychobiology of Depression (CDS) has followed a large cohort of individuals with mood disorders for over 20 years with assessments at semi-annual, and then annual, intervals. The observation period is now sufficient to address the above questions.

Methods

Subjects

Between 1978–1981, inclusive, investigators at five academic centers recruited inpatients and outpatients who met Research Diagnostic Criteria (RDC) (Spitzer RL *et al.*, 1978) for major depression, mania or schizoaffective disorder. Inclusion criteria specified that all participants were 18 years of age or older, knowledgeable of their biological parents, English-speaking, and Caucasian.

The following report is limited to subjects who completed at least 20 years of follow-up and who, before intake or at anytime during follow-up, met RDC for mania, hypomania, or schizoaffective disorder, manic type, other than the mainly schizophrenic subtype. In the RDC, the mainly schizophrenic subtype of schizoaffective disorder is equivalent to DSM-IV schizoaffective disorder but the remainder of RDC schizoaffective cases nearly all meet criteria for DSM-IV major depression or manic disorder with mood-incongruent psychotic features.

Procedures

After subjects provided informed consent carefully trained, professional raters used the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott J *et al.*, 1978) to establish current and lifetime diagnoses. The SADS ratings on which these were based integrated information from subject interview, medical record review, and informants when available. The SADS included a Global Assessment Scale (GAS), a 100-point rating that integrates symptom severity with impairment in functioning.

Raters conducted follow-up assessments semi-annually for the first five years and then annually. The Longitudinal Instrument for Follow-up Evaluation (LIFE) (Keller MB *et al.*, 1987), and later variants, the LIFE-II and SLICE, were used to record follow-up information from direct interviews and from medical record review. These instruments used psychiatric symptom ratings (PSRs) to track all RDC syndromes that had been active at intake or that developed during follow-up. Interviewers helped subjects identify points at which symptom levels had changed and then quantified the levels present between those points. For major depression, manic disorder, schizoaffective depression and schizoaffective mania these levels were assigned scores of “1” to “6”. A score of “1” indicated no symptoms, “2” indicated the presence or one to two symptoms to a mild degree, “5” indicated full syndrome and “6” a relatively severe, full syndrome. Scores of “3” and “4” indicated the continued presence of an episode with less than the number of symptoms necessary for an initial diagnosis. The end of an episode required eight consecutive weeks of PSR ratings no greater than “2” and a new episode required that the subject again met criteria for definite major depression, mania, or schizoaffective disorder.

Data Analytic Procedures

Age at intake was used to assign subjects *a priori* into youngest (18–29 years), middle (30–44 years) and oldest (over 44 years) groups. We used the proportion of weeks and episodes (symptom persistence) to quantify symptom activity over time and grouped the follow-up weeks into five-year periods. To test for evidence that depressive and manic/hypomanic symptoms showed differing patterns of change over time we conducted analyses separately for depression and manic/hypomanic poles. Subjects were deemed in an episode of depression if PSR ratings for major depression or schizoaffective depression exceeded “2” and were, likewise, considered to be in episodes of mania or hypomania if PSR ratings for mania, schizoaffective mania, or hypomania exceeded “2”.

An ANOVA was first used to determine whether the three age groups differed in symptom persistence across the entire 20 years of follow-up. A SPSS repeated-measures general linear model (GLM) procedure then tested for significant within-subject changes across the four follow-up periods, first with all age groups combined, and then for each age group separately.

Analyses next determined whether the age-of-onset, the age at which the subject first met criteria for a major depressive, schizoaffective or manic episode, predicted changes across follow-up periods in symptom persistence, first with the age-groups combined and then in each group separately. The relative importance of age at intake and age at onset was assessed in a logistic regression on system persistence over the entire 20 years. Because the distribution of symptom persistence values varied over time and across groups, we also examined the proportion of subjects who had episodes for greater than 50% of the weeks in each five-year time period. McNamar’s tests were used to compare the first and last follow-up periods by the proportions of subjects with that level of symptom persistence. We then assessed the degree with which symptom persistence in each five-year period predicted persistence in subsequent periods, and whether these relationships varied by age group. All

of the above procedures were repeated for the percent of time in manic or hypomanic episodes. Spearman tests were used for all correlations. All statistical tests used a two-tailed alpha and no correction was made for multiple testing.

Results

Baseline Status

The three age groups did not differ by sex, severity as measured by the Global Assessment Scale (GAS) at intake, proportions with schizoaffective disorder, or the presence of comorbid alcohol or drug dependence (Table 1). As expected, the three age groups differed significantly in having progressively later ages of onset.

Depressive Symptoms

The youngest, middle, and oldest groups were in depressive episodes for means (SD) of 24.4 % (30.0), 30.0 % (29.2), and 22.8% (29.2) percent of weeks, respectively, over the entire twenty years of follow-up ($F=0.812$, $df=2/145$, $p=0.446$). With age groups combined, GLM analyses showed an increasing persistence of depressive symptoms across the four, five-year periods ($F=7.1$, $p=0.008$). This pattern appeared in the youngest ($F=4.9$, $p=0.031$) and middle ($F=4.4$, $p=0.040$) age groups but not in the oldest ($F=0.24$, $p=0.626$) (Figure 1).

A depiction of the proportion of subjects in depressive episodes for over 50% of the weeks in each five-year period showed steady increases in the youngest and middle age groups (Figure 2). The likelihood of being depressed for the majority of weeks increased from the first to the last follow-up period by 53.4%, 37.4% and 19.7% in the youngest, middle and oldest groups, respectively. McNemar's tests showed the increase to be significant for the overall sample ($p=0.002$) and for the youngest ($p=0.039$) and middle ($p=0.049$) age-groups.

Sex did not predict symptom change with the age groups combined ($F=0.006$, $p=0.939$), nor did it predict in any of the three groups when these were tested separately. Likewise, sex was not significantly associated with persistence across the entire twenty-year follow-up.

When added to the GLM model, neither age-of-onset nor age at intake predicted changes in depressive symptom persistence over the twenty years of follow-up. When baseline age and age of onset were entered as independent variables in a linear regression analysis on symptom persistence over twenty years, however, a positive trend was noted for baseline age ($t=1.77$, $p=0.079$) and a strong negative relationship emerged for age of onset ($t=-2.68$, $p=0.008$). Symptom persistence was negatively, though not significantly, related to age at onset in the youngest ($t=-1.50$, $p=0.140$), middle ($t=-1.64$, $p=0.105$) and oldest ($t=-1.12$, $p=0.276$) groups while the relationship with age at onset was consistently positive though not significant ($t=0.164$, $p=0.87$; $t=0.90$, $p=3.72$; $t=0.129$, $p=0.899$, respectively).

An ROC analysis to indicate the age of onset that best identified subjects who would be in episodes for more than half of the follow-up period failed to reach significance (area under curve=0.426, SE=0.062, $p=0.203$).

Within-subject correlations in depressive symptom persistence across follow-up periods were highly significant (Table 2) and were similar in the three age groups. The means of all interval correlations for the youngest, middle and oldest groups were 0.652 (.156), 0.562 (.144) and 0.703 (.112), respectively ($F=1.60$, $df=2/15$, $p=0.234$). Correlations decreased across wider follow-up intervals; the mean (SD) correlation for contiguous five-year periods was 0.726 (.105) but was 0.605 (.109) for intervals separated by five years and 0.447 (.094) for intervals separated by ten years ($F=8.43$, $df=2/15$, $p=0.004$).

Manic/Hypomanic Symptoms

A trend was observed toward a decreasing persistence of manic/hypomanic symptoms across the three age groups, but inter-individual variation was high and group differences were not significant; mean (SD) values for the youngest, middle, and oldest groups were 10.8 % (18.1), 8.5 % (10.5), and 5.9 % (10.4), respectively, ($F=0.805$, $df=2/227$, $p=0.448$). There was no tendency for the proportion of weeks in manic/hypomanic episodes to increase or decrease across the four, five-year periods either for all age groups combined or within any of the three age groups (Figure 3). Neither age at study entry ($t=-0.701$, $p=0.484$) nor age at onset ($t=-0.487$, $p=0.627$) was associated with total percent time in manic or hypomanic episodes when both variables were entered in a logistic regression model.

Within-subject correlations in manic/hypomanic symptoms remained significant across follow-up intervals and, as with depressive symptoms, decreased as interval length increased from contiguous periods (mean=0.61, SD=0.26), to intervals of five years (mean=0.29, SD=0.18) and to intervals of ten years (mean=0.11, SD=0.13) ($F=7.5$, $df=2/15$, $p=0.006$). The means (SD) of all interval correlations did not differ significantly across age groups. For the youngest, middle and oldest group, they were 0.58 (.26), 0.25 (.18) and 0.43 (.34), respectively ($F=2.38$, $df=2/15$, $p=0.126$).

The mean correlations and symptom persistence across follow-up periods was significantly higher for depressive symptoms (0.64, SD=0.14) than for manic/hypomanic symptoms (0.44, SD=0.12) ($t=7.42$, $df=17.0$, $p=.000$). This was true as well for each age group individually.

Discussion

Twenty years of annual assessments revealed substantial increases in the proportion of weeks spent in depressive episodes, and corresponding increases in the likelihood of symptom chronicity, as follow-up progressed, patterns that held for the two age groups younger than 45 years at the study's beginning but not for the oldest group. Earlier age-of-onset was strongly associated with total time depressed through 20 years of follow-up and this relationship persisted across the three age groups. However, no clear age-of-onset threshold was apparent below which the likelihood of subsequent chronicity increased markedly. Manic and hypomanic symptom persistence, on the other hand, showed no clear change over time and was not affected by age at onset.

These findings indicate that the poorer outcomes associated with early ages of onset in previous studies (Carlson GA *et al.*, 2000; Tohen M *et al.*, 2000; McElroy SL *et al.*, 2001; Carlson GA *et al.*, 2002; Carter TD *et al.*, 2003; Ernst CL *et al.*, 2004) were not due to the effects of current age. An early age at onset, rather than youth itself, appears to portend higher levels of depressive morbidity, an effect that does not lessen over several decades. Yet, age at onset did not predict a worsening in symptom persistence. Rather, increases in depressive morbidity occurred in the youngest and middle age groups regardless of age at onset. This suggests that either the passage of time or the cumulative effects of active illness, but not the process of growing old, leads to increased depressive morbidity.

The group that was 45 years or older at the beginning of follow-up did not experience the increases in depressive morbidity seen in the two younger groups. We had no *a priori* prediction that changes in symptom persistence over time would apply to only some age groups. This group was also the smallest and had only begun to enter the age range typically considered geriatric. The follow-up of this sample is continuing and it is, of course, aging. Future analyses will determine whether the manifestations of bipolar disorder truly change as individuals enter this important period.

The higher symptom persistence associated with an early age of onset, as well as the tendency to worsen over time, were seen with depressive symptoms but not with manic/hypomanic symptoms. Thus, the poorer prognosis experienced by individuals with early onset illness is driven by depressive morbidity and, regardless of age at onset, morbidity tends to be increasingly dominated by depressive symptoms as time passes.

The within-subject correlations between both depressive and manic/hypomanic symptom persistence remain significant over long time periods and suggest that the proportion of time spent in either phase is a quality of an individual's life-long illness that declares itself early. On the other hand, the observation that these correlations decrease with longer intervals suggests that individuals also pass through periods characterized by symptom persistence that is higher or lower than at other periods of their lives.

The significantly greater correlations in depressive symptom persistence across time periods that we noted in the oldest group of the CDS unipolar cohort (Coryell W *et al.*, Submitted) were absent here. Total correlations for middle and oldest unipolar groups were 0.51 (0.13) and 0.66 (0.10), respectively and were not dissimilar from the corresponding figures for depressive symptoms described here for the bipolar group, 0.56 (0.14) and 0.70 (0.11). Correlations for the youngest unipolar and bipolar groups were 0.44 (0.15) and 0.65 (0.16), respectively ($t =$, $df =$, $p =$). We had no *a priori* hypothesis regarding these patterns and their implications are limited pending replication. A tentative interpretation is that the high rate of life events that characterizes early adulthood may shape the course of unipolar depression more than bipolar disorder.

In summary, these data provide evidence that, in adult bipolar illness, depressive symptoms become more persistent over decades in younger adults while manic and hypomanic symptoms do not, and that an early age of onset predicts higher long-term depressive morbidity but not a deteriorating course. The degree to which either manic or depressive symptoms persist in a five-year period appears to be a stable characteristic of an individual though this stability lessens over time.

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Figure 1.
Proportion of Weeks in Depressive Episodes

Figure 2.
Percent of Subjects in Depressive Episodes for Majority of Weeks

Figure 3.
Percent of Time in Manic/Hypomanic Episodes

Table 1**Status at Intake by Age-Grouping**

	Youngest (18–29)	Middle (30–44)	Oldest (45)
n	56	68	24
number (%) female	32 (57.1)	44 (64.7)	19 (79.2)
mean (SD) age ¹	24.2 (3.4)	36.0 (4.1)	50.3(4.9)
mean (SD) age at end of follow-up ¹	44.2 (3.4)	56.0 (4.1)	70.0 (4.9)
mean (SD) age at onset ¹	19.2 (4.4)	24.0 (6.5)	65.5 (12.3)
number (%) inpatient	48 (85.7)	58 (85.3)	22 (91.7)
mean (SD) educational level	3.2 (1.0)	3.0 (1.3)	3.6 (0.7)
mean (SD) GAS score	37.5 (9.9)	38.3 (12.4)	39.2 (10.2)
marital status, number (%) ³			
never married	44 (78.6)	11 (16.2)	1 (4.2)
married	7 (12.5)	41 (60.3)	13 (54.2)
divorced/separated	5 (8.9)	16 (23.5)	8 (33.3)
widowed	0	0	2 (1.4)
number (%) schizoaffective	11 (19.6)	8 (11.8)	2 (8.3)
number (%) ever drug abuse	6 (10.7)	6 (8.8)	0 (-)
number (%) ever alcoholic	15 (26.8)	18 (26.5)	2 (8.3)
number (%) delusional	31 (55.8)	32 (47.1)	10 (41.7)
Index episode:			
number (%) mania	38 (67.9)	39 (57.4)	18 (75.0)
number (%) depressed	38 (67.9)	44 (64.7)	16 (66.7)
number (%) cycling	15 (26.8)	20 (29.4)	11 (45.8)
number (%) mixed	1 (1.8)	3 (4.4)	0 (-)

¹F = 373.8, $p=0.000$

²F=43.9, $p=0.000$

³ $\chi^2=76.5$, $df=6$, $p=0.000$

Table 2
Relationships between Subsequent Follow-Up Periods in Percent Time in Episodes

<u>Depressive</u>	<u>youngest</u>			<u>middle</u>			<u>oldest</u>		
	Years 6–10	Years 11–15	Years 16–20	Years 6–10	Years 11–15	Years 16–20	Years 6–10	Years 11–15	Years 16–20
Years 1–5	.53 [†]	.56 [†]	.48 [†]	.66 [†]	.44 [†]	.34 ^{**}	.73 [†]	.74 [†]	.52 ^{**}
Years 6–10		.75 [†]	.70 [†]		.68 [†]	.56 [†]		.84 [†]	.63 [†]
Years 11–15			.89 [†]			.69 [†]			.76 [†]
<u>Manic</u>									
Years 1–5	.59 [†]	.28 [*]	.22	.52 [†]	.39	.27	.46 [*]	.39	.27
Years 6–10		.65 [†]	.50 [†]		.50 [*]	.40 [*]		.50 [*]	.40 [*]
Years 11–15			.48 [†]			.51 [*]			.51 [*]

* Spearman correlation, $p < .05$

** Spearman correlation, $p < .01$

[†] Spearman correlation, $p < .001$