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Brief Report

Phenomenology associated with age at onset in patients with bipolar disorder at their first psychiatric hospitalization

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Objective: To compare the clinical presentation of patients with early-onset (age < 18 years) and typical-onset (age 20–30 years) bipolar disorder at the time of first hospitalization.

Methods: Patients, aged 12–45 years at their first psychiatric hospitalization, with a DSM-IV diagnosis of bipolar disorder, manic or mixed, were evaluated on measures of manic, depressive, and positive psychotic symptoms. Differences in symptom profiles between early- and typical-onset groups were examined.

Results: One hundred three early-onset and 58 typical-onset patients were compared. Mixed episodes were more common in the early-onset group, while psychotic features and current substance use were more common in the typical-onset group. There was no significant difference in manic symptom severity ratings between early- and typical-onset groups ($F = 1.8$, df = 11, 144, $p = 0.06$). However, these groups differed in depressive ($F = 4.2$, df = 16, 139, $p < 0.001$) and positive psychotic ($F = 2.8$, df = 16, 139, $p = 0.001$) symptom profiles. Typical-onset bipolar patients reported more severe weight loss and formal thought disorder compared with early-onset patients.

Conclusions: Depressive and positive psychotic symptoms may differ in association with age at onset among patients with bipolar disorder. Additional studies are necessary to determine whether homogeneous phenotypes of bipolar disorder can be delineated based upon age at onset.

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Studies examining the relationship of age at onset and the clinical presentation of bipolar disorder have produced inconsistent results, which may be partially explained by differences in methodologies (1–4). For example, age cutoffs to define early-, adult-, and late-onset bipolar disorder are often arbitrarily chosen, rather than using onset distributions determined by systematic evaluation of a large sample of patients (5). From a sample of 579 bipolar patients, Bellivier et al. (6) identified three sub-groups defined by age at onset: early-onset [mean age at onset = 17.4 (2.3) years], intermediate-onset [25.1 (6.2) years], and late-onset [40.4 (11.3) years]. Using cutoffs to represent these distributions, we compared the phenomenology of patients with bipolar disorder at their first hospitalization for an affective episode. Based upon a previous study (3), we hypothesized that early-onset patients would be more likely to

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present with a mixed episode, while typical-onset patients would be rated with more severe positive psychotic symptoms.

Patients and methods

Patients were recruited as part of the University of Cincinnati First-Episode Mania Study (7). After full description of study procedures, written informed consent was provided by all subjects or their legal guardians. The study was approved by the institutional review boards of the University of Cincinnati and Cincinnati Children's Hospital Medical Center. For the current analysis, all subjects were required to have a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of bipolar I disorder, manic or mixed, with or without psychotic features (delusions or hallucinations as described in the DSM-IV); be between 12 and 45 years of age at admission; have no prior psychiatric hospitalizations; and be able to communicate in English. Patients were excluded if symptoms were due to an acute medical illness, or acute intoxication or withdrawal from drugs or alcohol.

DSM-IV diagnoses of bipolar disorder, manic or mixed, with or without psychotic features were established in patients above the age of 18 years using the Structured Clinical Interview for DSM-IV, Patient Edition, by experienced investigators with good interrater reliability ($\kappa > 0.90$) (7, 8). In patients aged 12–18 years, diagnostic interviews of patients and their legal guardians were performed using the Washington University at St Louis Kiddie-Schedule for Affective Disorders and Schizophrenia by trained child and adolescent psychiatrists with established diagnostic reliability ($\kappa = 0.94$) (9, 10). Psychiatric symptoms were assessed using the Young Mania Rating Scale (YMRS), 17-item Hamilton Rating Scale for Depression (HAM-D), and the Scale for the Assessment of Positive Symptoms (SAPS) (11–13). The investigators demonstrated good interrater reliability for symptom measures (intraclass correlation coefficient >0.70 for most individual symptoms and all total scores) (7).

Age at onset was defined as the age at which patients endorsed enough DSM-IV syndrome criteria for an affective episode (either a major depressive, manic, or hypomanic episode). Based on the distributions identified by Bellivier et al. (6), patients were grouped as: early-onset (<18 years old), typical-onset (20–30 years old), or late-onset (>35 years old). Only early- and typical-onset patients were evaluated, as the number of late-onset patients ($n = 12$) was too small for comparison. For all patients, the current episode represented the first requiring psychiatric hospitalization. However, the current episode was not necessarily the first affective episode experienced by the patient. Of the total sample, 42 (26%) patients reported one previous untreated episode, and 30 (19%) reported two or more untreated episodes. Of those subjects reporting a prior affective episode, 42 (58%) stated they experienced a depressive episode, and 25 (35%) stated they had a manic episode. Eighteen (25%) reported a prior mixed episode. Current alcohol and substance use was assessed, and demographic data were obtained from patient and/or legal guardian interviews and medical records.

Differences in manic, depressive, and positive psychotic symptoms associated with the current episode (i.e., the first affective episode requiring psychiatric hospitalization) between early- and typical-onset bipolar patients were analyzed using multivariate analysis of covariance (MANCOVA), adjusting for sex, ethnicity, type of episode (manic or mixed), current alcohol/substance use, and number of previous untreated episodes (categorical: 0, 1, 2, or 3 or more). Symptoms that were endorsed by less than 15% of the sample and had no significant group differences were removed; these included one HAM-D (genital symptoms) and 12 SAPS items: (voices commenting; voices conversing; somatic and tactile hallucinations; olfactory hallucinations; jealousy, sin or guilt, somatic, insertion, and withdrawal delusions; repetitive bizarre behavior; and, incoherent and clanging formal thought disorder). Significance of the omnibus MANCOVAs was defined as a $p < 0.05$. As MANCOVA provides overall differences in symptom profiles between groups but does not show the direction of differences, effect sizes (d_s) for individual items were calculated to determine which specific symptoms contributed to differences between early- and typical-onset groups, and group means of individual items were examined to determine the direction of differences.

Results

In total, 103 early- and 58 typical-onset patients with bipolar disorder were analyzed. Demographic and clinical variables are presented in Table 1. The early-onset group had a higher percentage of white patients than the typical-onset group. There was no difference in sex distribution ($\chi^2 = 1.5$, df = 1, $p = 0.2$). The early- and typical-onset groups did not differ in the distribution of the number of previous untreated episodes experienced ($\chi^2 = 2.1$, df = 3, $p = 0.6$). However, a higher percentage of patients in the early-onset group reported experiencing a

Table 1. Demographic, diagnostic, and symptom variables among patients with early- and typical-onset bipolar disorder

Variable	Early-onset (N = 103)	Typical-onset (N = 58)
Age at onset, mean (SD)	13.2 (3.3)	24.2 (3.5)
Age at assessment, mean (SD)	17.2 (5.1)	26.1 (5.2)
Female, n (%)	53 (51.5)	24 (41.4)
Caucasian[a], n (%)	81 (78.6)	36 (62.1)
Number of previous untreated episodes, n (%)		
0	59 (57.3)	30 (51.7)
1	26 (25.2)	16 (27.6)
2	5 (4.9)	6 (10.3)
3 or more	13 (12.6)	6 (10.3)
Polarity of first affective episode[b], n (%)		
Manic	27 (26.2)	29 (50.0)
Mixed	48 (46.6)	9 (15.5)
Depressed	24 (23.3)	19 (32.8)
Diagnosis of current episode requiring hospitalization, n (%)		
Mixed episode[c]	69 (67.0)	17 (29.3)
Psychotic features[d]	56 (54.4)	50 (86.2)
Alcohol/substance use[e], n (%)	24 (23.8)	24 (41.4)
Hamilton Depression Rating Scale, mean (SD)		
Weight loss	0.2 (0.8)	1.0 (0.8)
Psychomotor retardation	0.6 (0.8)	0.1 (0.8)
Late insomnia	0.7 (1.0)	1.2 (1.0)
Scale for the Assessment of Positive Symptoms, mean (SD)		
Circumstantiality	1.0 (1.4)	2.3 (1.4)
Tangentiality	0.9 (1.4)	2.0 (1.4)
Derailment	0.8 (1.4)	1.7 (1.5)
Religious delusions	0.6 (1.4)	1.5 (1.4)
Illogicality	0.6 (1.3)	1.3 (1.4)

[a] $\chi^2 = 5.1$, df = 1, p = 0.02.
[b] $\chi^2 = 17.4$, df = 3, p = 0.001.
[c] $\chi^2 = 21.2$, df = 1, p < 0.001.
[d] $\chi^2 = 16.7$, df = 1, p < 0.001.
[e] $\chi^2 = 5.4$, df = 1, p = 0.02.

mixed episode as their first affective episode compared with the typical-onset group. A higher percentage of patients in the typical-onset group reported experiencing a manic episode as their first affective episode.

When comparing the clinical presentation of the current episode requiring their first psychiatric hospitalization, the early-onset group had a significantly higher percentage of patients with a mixed episode compared with the typical-onset group. In the early-onset group, patients presenting with a mixed episode were less likely to have a history of/or current alcohol/substance use compared with those presenting with a manic episode ($\varphi = 0.2$, p = 0.02). There was no relationship between type of episode and alcohol/substance use in the typical-onset group ($\varphi = -0.04$, p = 0.8). In both groups, there was no relationship between type of episode and prior antidepressant use (early-onset: $\varphi = -0.2$, p = 0.09; typical-onset: $\varphi = -0.2$, p = 0.2). A lower percentage of early-onset patients were diagnosed with psychotic features (either delusions or hallucinations as described in the DSM-IV) than that in the typical-onset group. Psychosis was significantly related to the type of episode ($\varphi = 0.3$, p < 0.001), as patients with a manic episode were more likely to have psychosis. Current alcohol/substance use was higher in the typical-onset group, which may be related to having a longer duration of illness. Current alcohol/substance use was not related to the presence of psychotic features ($\varphi = 0.1$, p = 0.2).

MANCOVA showed no significant difference in manic symptom ratings between early- and typical-onset groups ($F = 1.8$, df = 11, 144, p = 0.06). These groups did, however, differ in depressive ($F = 4.2$, df = 16, 139, p < 0.001) and positive psychotic ($F = 2.8$, df = 16, 139, p = 0.001) symptom profiles. HAM-D and SAPS items contributing to differences between early- and typical-onset groups with moderate to large effect sizes ($d_s > 0.5$) are listed in Table 1. On the HAM-D scale, the typical-onset group reported less severe psychomotor retardation ($d_s = 0.62$), but more severe weight loss ($d_s = 0.93$) and late insomnia ($d_s = 0.51$). On the SAPS scale, typical-onset patients demonstrated more severe circumstantiality ($d_s = 0.99$), tangentiality ($d_s = 0.76$), derailment ($d_s = 0.66$), religious delusions ($d_s = 0.66$), and illogicality ($d_s = 0.51$).

Discussion

Our results suggest that early-onset bipolar patients may be more likely to present with mixed episodes, and less likely to present with psychotic features compared with typical-onset bipolar patients at their first psychiatric hospitalization. There may be heterogeneity of depressive and positive psychotic symptoms associated with age at onset, as patients with typical-onset may exhibit more severe weight loss and formal thought disorder.

Our first hypothesis, that early-onset bipolar patients would be more likely to present with a mixed episode, was confirmed. As the majority of the early-onset group (72%) was under the age of 18 years at the time of assessment, this finding is consistent with published reports suggesting high rates of mixed mania in adolescent bipolar disorder (14, 15). Our second hypothesis, that typical-onset patients would be rated with more severe psychotic features, was also confirmed. A higher percentage of typical-onset patients experienced a manic episode, and therefore may be more likely to present with positive formal thought disorder compared to those experiencing a mixed episode (16). It is possible that the characterization of

positive formal thought disorder, particularly in the typical-onset group, may be more consistent with schizophrenia spectrum disorders or partially attributable to substance abuse (17).

There is inconsistent evidence regarding rates and severity of psychosis among early- and adult-onset patients with bipolar disorder (2–4), which may be partially explained by differences in study methodologies. For example, rates of psychosis may be higher among inpatient subjects compared with outpatient subjects (3, 4). Diagnostic interview methods may also affect rates of psychosis in younger patients with bipolar disorder (18), and differences in assessment methods (retrospective versus prospective) may result in inconsistencies between studies. As mentioned previously, cutoffs used to define age at onset groups are variable across studies and no valid definitions of age at onset groups have been established (19); it is unclear to what extent this may affect the characterization of early- and adult-onset groups.

These results should be viewed in the context of the study's limitations. First, generalizability of the results may be limited as subjects were recruited from a single treatment site. Since only hospitalized subjects were assessed, the results may also not be generalized to outpatient populations. Second, the definition of age at onset may have been subject to recall bias, and may have included the prodromal phase of the patient's illness. Furthermore, the number and types of previous untreated episodes were subject to recall bias and the current episode may not have been reflective of the patient's first affective episode. Third, cutoffs for onset groups were based upon distributions reported in one study (6), and we did not include late-onset patients in the analyses because the number of subjects in that group was too small for an adequately powered statistical comparison. Additional studies are needed to confirm the delineation of these sub-groups. Using empirically derived onset distributions, studies using consistent methodologies are needed to determine whether age at onset is, indeed, associated with specific clinical characteristics and differences in severity of bipolar symptoms.

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