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INCREASED PROSPECTIVE HEALTH SERVICE USE FOR DEPRESSION AMONG ADULTS WITH CHILDHOOD ONSET BIPOLAR DISORDER

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Abstract

Objective—To examine the prospective relationship between age of onset of bipolar disorder and the demographic and clinical characteristics, treatment, new onset of psychiatric comorbidity, and psychosocial functioning among adults with bipolar disorder.

Study design—As part of the National Epidemiologic Survey on Alcohol and Related Conditions, 1600 adults who met lifetime *DSM-IV* criteria for bipolar disorder-I (n=1172) and bipolar disorder-II (n=428) were included. Individuals were evaluated using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-*DMS-IV* Version and data was analyzed from Waves 1 and 2, approximately 3 years apart. Individuals with bipolar disorder were divided into three age at onset groups: childhood (<13 years old, n=115), adolescence (13-18 years old, n=396), and adulthood (>19 year old, n=1017).

Results—After adjusting for confounding factors, adults with childhood-onset bipolar disorder were more likely to see a counselor, have been hospitalized and have received emergency room treatment for depression compared with those with adulthood-onset bipolar disorder. By contrast, there were no differences in the severity of mania or hypomania, new onset of comorbidity, and psychosocial functioning by age of bipolar disorder onset.

Conclusions—Childhood-onset bipolar disorder is prospectively associated with seeking treatment for depression, an important proxy for depressive severity. Longitudinal studies are needed in order to determine whether prompt identification, accurate diagnosis, and early

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intervention can serve to mitigate the burden of childhood onset on the long-term depressive burden of bipolar disorder.

The onset of bipolar disorder in childhood and adolescence is increasingly recognized to be associated with greater illness severity, poorer outcome, [1-3] and serious disruption of the development and emotional growth of the youth. [4] Compared with adult-onset bipolar disorder, childhood- and adolescent-onset bipolar disorder has been associated with more episodes and greater severity of mania and depression, earlier recurrence of mood episodes after initial remission, ultradian cycling, fewer days of euthymia, greater delays to first treatment contact, more comorbidities and suicide attempts, greater impairment in functioning and quality of life, and higher health care costs.[1, 5-9] Most of the studies that have compared the age at onset of bipolar disorder have relied on clinical samples, whose results may not generalize to the broader population of individuals with bipolar disorder. To our knowledge there are no published prospective epidemiological studies examining the course of bipolar disorder by age at onset of bipolar disorder. Given the clinical relevance and potential prognostic implications of childhood-onset bipolar disorder, we sought to build on prior cross-sectional work, [10] by drawing on the longitudinal design of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) to examine the course of bipolar disorder-I (one or more manic or mixed episodes; severe impairing) and bipolar disorder-II (at least one hypomanic episode; less severe) by age at onset of bipolar disorder. We hypothesized that compared with individuals with adult-onset bipolar disorder, adults with childhood-onset bipolar disorder would have: 1) greater number and length of hypomanic/manic and depressive episodes and lower rates of recovery from both; 2) higher rates of treatment seeking for hypomania/mania and depression; 3) higher incidence of psychiatric comorbidity and lower psychosocial functioning.

METHODS

The NESARC [11, 12] is a longitudinal nationally representative survey based on the civilian, non-institutionalized population of the 50 United States, age 18 and over. Data collection was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and was conducted in two waves using face-to-face interviews. Wave 1 interviews (n = 43,093) were conducted between 2001 and 2002 by trained lay-interviewers who had an average of five years experience working on census and other health-related national surveys. [11] The current study utilized data from Wave 1 as well as Wave 2 interviews, which were conducted between 2004 and 2005 with 34,653 of the NESARC Wave 2 respondents. [12] After accounting for those ineligible for the Wave 2 interview (e.g., deceased), the response rate for Wave 2 was 86.7%. The mean interval between Wave 1 and Wave 2 interviews was 36.6 (SD=2.62) months. The research protocol, including informed consent procedures, received full human subjects review and approval from the U.S. Census Bureau and the U.S. Office of Management and Budget. Informed consent was obtained from all participants before beginning the interviews. Detailed descriptions of methodology, sampling, and weighting procedures can be found elsewhere. [11]

The number of participants included in the present study (n=1,598) were those with lifetime diagnosis of bipolar disorder-I (n=1,172) and bipolar disorder-II (n=426) in Wave 1 based on age of onset of mania or hypomania. By contrast, in our prior cross-sectional study, [10] we included only those participants with lifetime diagnosis of bipolar disorder-I (n=1,411) based on age of onset of mania to determine bipolar disorder onset age. To be consistent with previous studies, [6, 10] respondents with lifetime diagnosis of bipolar disorder-I and bipolar disorder-II (n=428) in Wave 1 were divided into three groups: childhood (<13 years old, 8.92% n=115), adolescence (13-18 years old, 28.14%, n=396), and adulthood (>19 years old, 62.94%, n=1017).

Sociodemographic measures included age, sex, race/ethnicity, marital status, education, employment status and personal income.

All diagnoses were made according to DSM-IV criteria using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-Version for DSM-IV (AUDADIS-IV), a valid, reliable, fully structured diagnostic interview designed for use by professional interviewers who are not clinicians. [13] Reliability is fair for the bipolar disorder-I diagnosis ($\kappa = 0.59$), good for bipolar disorder-II ($\kappa = 0.69$), [14] and is excellent for alcohol diagnoses ($\kappa = 0.74$) and drug diagnoses ($\kappa = 0.79$). [15] The anxiety disorders included in the present study are social anxiety disorder, panic disorder, and generalized anxiety disorder, which have fair to good reliability ($\kappa = 0.42-0.52$). [15]

Based on the findings of previous studies, we compared the following by age at onset of bipolar disorder: (1) demographic characteristics; (2) clinical characteristics of bipolar disorder, including course of symptoms and treatment utilization between Wave 1 and Wave 2; (3) incidence of psychiatric comorbidities between Wave 1 and Wave 2; and (4) psychosocial functioning at Wave 2, as assessed by the mental health, social functioning, and role emotional subscales, as well as the mental component summary of the 12-item Short Form Health Survey, version 2 (SF-12), a reliable and valid measure of disability used in population surveys. [16]

Statistical analyses

Weighted percentages and means were computed to derive associations with prospectively ascertained comorbidities, treatment, and level of functioning among respondents with bipolar disorder by age at onset. To be consistent with our prior research [10], we used the 6 month cut off point for the duration of the episodes. Because the combined standard error of 2 means or percentages is always equal to or less than the sum of the standard errors of those 2 means, we conservatively consider that two confidence intervals (CIs) that do not overlap to be significantly different from one another. [17] Multinomial logistic regression was used to obtain adjusted odds ratios (AORs) for new onset of comorbidities, functioning, clinical characteristics of bipolar disorder, and treatment for bipolar disorder adjusted for age, sex, race and income. Multiple linear regression was used to obtain adjusted means for continuous variables. All p-values are based on two-tailed tests with $\alpha = 0.05$. All analyses, including parameter estimates, standard errors and 95% confidence intervals (95% CIs) were performed using SUDAAN to adjust for the complex design of the NESARC.

RESULTS

Compared with adult-onset bipolar disorder, childhood- and adolescent-onset bipolar disorder was associated with lower odds of being female and of being married or cohabiting (Table I; available at www.jpeds.com). In addition, compared with adult-onset bipolar disorder, childhood-onset bipolar disorder was associated with lower odds of being Hispanic and of having higher education, whereas adolescent-onset bipolar disorder was associated with lower personal income and lower odds of family history of alcohol abuse or dependence.

Childhood- and adolescent-onset of bipolar disorder were associated with lower age of onset of depression and more mania onset first than depression compared with those with adult-onset bipolar disorder (Table II; available at www.jpeds.com).

Compared with adult-onset of bipolar disorder, childhood-onset of bipolar disorder was associated with greater odds of having received any treatment for depression between Waves 1 and 2, including seeing a counselor, having been hospitalized for depression, and

having sought emergency room treatment. By contrast, there were no differences in the probability or type of treatment between individuals with adolescent- versus adult-onset bipolar disorder. In addition, there were no differences in the clinical characteristics of bipolar disorder or in the treatment for mania or hypomania among individuals by age at onset of bipolar disorder (Table II).

In addition, a subanalysis of the clinical characteristics and treatment for depression at Wave 1 found that compared with adult-onset of bipolar disorder, childhood- and adolescent- onset of bipolar disorder was associated with higher number of depressive episodes (childhood vs. adulthood: 8.06 vs. 6.72; AOR=3.02; $p=0.05$; adolescence vs. adulthood: 8.96 vs. 6.72; AOR= 3.93; $p=0.01$).

There were no differences in the incidence of psychiatric comorbidity or in the level of psychosocial functioning by age at onset of bipolar disorder (Table III; available at www.jpeds.com).

DISCUSSION

In a large epidemiological sample of individuals with bipolar disorder followed prospectively for three years, adults with childhood-onset bipolar disorder were more likely to see a counselor, have been hospitalized and have received emergency room treatment for depression compared with those with adulthood-onset bipolar disorder.

Confirming evidence from prospective clinical studies, [6-8] we found that adults with childhood-onset bipolar disorder had greater burden of depression as indicated by their higher rates of treatment seeking for depression and higher number of depressive episodes at baseline. By contrast, age of bipolar disorder onset was not associated with differences in the rate of treatment for mania or hypomania. Taken together, these findings suggest that childhood-onset bipolar disorder is associated with greater depressive, but not hypo/manic severity in adulthood. Childhood-onset bipolar disorder may be more likely to “burn out” of mania and progress into more severe depression during the follow-up compared with the adolescent- or adult-onset bipolar disorder.

Indeed, previous studies suggest that the burden of bipolar disorder depression is greater later in the illness. [18-21] A clinical prospective study of 529 adults with bipolar disorder-I and bipolar disorder-II showed that the significant differences seen after 1 year of follow-up in severity of mania and ultradian cycling in the childhood-onset bipolar disorder group were attenuated after 4 years of follow-up and but remained significant for severity and duration of depression and days euthymic. [7, 8] The authors concluded that early-onset bipolar disorder and delayed treatment were the most closely associated with measures of depression as adults, suggesting 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. [8]

Contrary to our initial hypotheses, we did not find significantly higher incidence of comorbidity or greater psychosocial impairment among adults with childhood-onset bipolar disorder compared with adult-onset bipolar disorder. This may be explained by the fact that there were high rates of new onset of comorbidity and low level of functioning among all three groups. In addition, contrary to prior clinical studies, [1, 22, 23] we found that childhood- and adolescent-onset bipolar disorder were associated more frequently with manic polarity of onset first than depressive polarity of onset compared with those with adult-onset bipolar disorder. These discrepancies may be due to differences between clinical and community samples.

The disruptions associated with bipolar disorder episodes during childhood and adolescence are likely to have a lasting impact on the child's developmental trajectory, limiting their ability to achieve critical social and professional developmental capabilities. [4] From a clinical perspective, it is of utmost importance to identify and treat children with bipolar disorder, particularly because between one-third and one-half of adults with bipolar disorder recall the onset of their symptoms during childhood or adolescence as we also found in our study. [4, 6, 24] The early recognition of bipolar disorder is of particular importance as youth are often diagnosed only years after the onset of the illness. This could lead to longer duration of untreated bipolar disorder, and in turn to greater chronicity of the illness and more social impairment. [25] In addition to the challenges of accurate and timely diagnosis, there is the challenge of efficacious treatment. First-line treatments for bipolar depression in adults may be no more efficacious than placebo when prescribed for bipolar depression among youth. [26] Whether or not these developmental differences are subserved by neurobiological differences is uncertain, however there is a clear need for efficacious pharmacological and psychosocial treatments for bipolar depression among youth. It is important to note that quetiapine, arguably the leading pharmacological treatment for depression among adults with bipolar disorder, may not be more efficacious than placebo among adolescents with bipolar disorder. [26, 27] As such, psychosocial treatments may be especially important among youth with bipolar disorder. [28] Recent randomized controlled trial studies supports the use of Family-Focused Treatment [29] and Dialectical Behavior Therapy [30] for reducing depressive burden among adolescents with bipolar disorder.

The potential limitations of this study should be taken into consideration. First, like in all large epidemiological studies, the NESARC interviews were conducted by lay professional interviewers rather than clinicians. However, the NESARC interviewers received extensive training with a highly structured and well-validated diagnostic assessment instrument. [31] Second, not all respondents from Wave 1 were able to be interviewed in Wave 2, however, statistical adjustments were made for nonresponse. Furthermore, although not all respondents were available for re-interview, the response rate of Wave 2 was 86.7%, [32] a much higher figure than other nationally representative surveys. Finally, the use of retrospective report to determine age at onset may be subject to recall bias. However, the proportion of individuals who reported childhood and adolescent onset of bipolar disorder is similar to those reported in other studies. [6]

Despite these limitations, this national study examined prospectively the course of bipolar disorder by age of onset. Our findings highlight the existence of developmental differences in the course of bipolar disorder with childhood onset conferring significantly increased depressive burden well into adulthood. Although bipolar disorder is widely recognized as a severe mental disorder, our prospective data contribute new information documenting the additional burden associated with its childhood-onset and the depressive predominance in adulthood. Longitudinal studies are needed in order to determine whether prompt identification, accurate diagnosis, and early intervention can serve to mitigate the effect of childhood onset on the long-term depressive burden of bipolar disorder.

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Table 1
Demographic Characteristics and Family History among individuals with Bipolar Disorder by Age Onset Bipolar Disorder

	Childhood <13 years old			Adolescence 13-18 years old			Adulthood 19+ years old			Childhood vs. Adulthood(ref)			Adolescence vs. Adulthood(ref)		
	MEAN or %	SE		MEAN or %	SE		MEAN or %	SE		OR/t-test	CI/p-value		OR/t-test	CI/p-value	
	N=115; %=8.92			N=396; %=28.14			N=1017; %=62.94								
Age	29.97	1.15		29.30	0.88		41.19	0.49		-9.19	<0.0001		-11.96	<0.0001	
Sex (female)	41.85	5.44		48.59	2.88		60.67	1.75		0.47	0.29	0.76	0.61	0.46	0.81
Race															
White	76.70	4.48		72.60	2.49		68.96	2.55		1.00	1.00	1.00	1.00	1.00	1.00
Black	9.40	3.15		12.05	1.79		12.05	1.18		0.70	0.32	1.53	0.95	0.66	1.38
Native American	3.30	1.71		3.75	1.17		4.50	1.06		0.66	0.19	2.26	0.79	0.35	1.77
Asian	4.73	2.42		2.41	0.97		2.85	1.06		1.49	0.45	4.93	0.80	0.29	2.26
Hispanic	5.88	1.87		9.19	1.48		11.65	2.00		0.45	0.21	0.98	0.75	0.47	1.20
Marital Status															
Married/cohabiting	41.50	5.22		34.78	3.27		58.93	1.69		0.49	0.31	0.79	0.37	0.27	0.52
Other	58.50	5.22		65.22	3.27		41.07	1.69		1.00	1.00	1.00	1.00	1.00	1.00
Education															
> High school graduate	41.89	5.41		49.21	3.20		55.85	2.09		0.57	0.36	0.91	0.77	0.55	1.06
Other	58.11	5.41		50.79	3.20		44.15	2.09		1.00	1.00	1.00	1.00	1.00	1.00
Employment Status (employed)	56.52	5.74		65.89	3.25		64.41	1.93		0.72	0.44	1.17	1.07	0.76	1.49
Personal Income															
<\$19,999	67.82	5.43		68.50	2.78		52.77	1.96		1.00	1.00	1.00	1.00	1.00	1.00
\$20,000-34,99	17.89	3.84		19.46	2.37		23.63	1.59		0.59	0.33	1.05	0.63	0.45	0.90
\$35,000-69,999	9.63	3.18		10.08	1.74		19.34	1.49		0.39	0.17	0.87	0.40	0.26	0.61
>\$70,000	4.66	2.74		1.97	0.79		4.26	0.77		0.85	0.23	3.12	0.36	0.15	0.85
Family History															
Depression	67.99	5.66		67.89	3.03		71.33	1.61		0.85	0.50	1.46	0.85	0.62	1.16
Alcohol Abuse or Dependence	53.39	6.11		47.68	3.09		60.73	1.81		0.74	0.44	1.24	0.59	0.44	0.79
Drug Abuse or Dependence	32.03	4.85		32.69	3.12		38.05	1.82		0.77	0.48	1.24	0.79	0.58	1.08
Antisocial Personality Disorder	54.15	5.87		49.70	3.18		47.30	1.89		1.32	0.81	2.13	1.10	0.82	1.48

Table 2
Clinical Characteristics and Treatment among individuals with Bipolar Disorder by Age Onset Bipolar Disorder

	Childhood <13 years old		Adolescence 13-18 years old		Adulthood 19+ years old		Childhood vs. Adulthood(ref)		Adolescence vs. Adulthood(ref)	
	MEAN or %	SE	MEAN or %	SE	MEAN or %	SE	AOR/ *	CI/p-value *	AOR/ *	CI/p-value *
Clinical Characteristics (since Wave 1)										
Age of onset of depression (Wave 1)	17.98	1.02	17.91	0.46	27.11	0.47	-5.15	<0.0001	-4.73	<0.0001
Order of onset of mania and depression (Wave 1)										
Depression first	7.58	2.74	26.98	2.67	43.51	1.92	0.06	0.02	0.30	0.20
Same year of onset	8.72	3.30	18.40	2.15	18.67	1.53	0.19	0.09	0.63	0.41
Mania first (or only) (ref)	83.70	3.98	54.62	2.91	37.82	1.89	1.00	1.00	1.00	1.00
Number of depressive episodes	3.53	0.50	3.23	0.29	2.95	0.18	0.55	0.3174	0.23	0.5167
Length of depression	32.07	9.79	18.72	4.62	25.16	2.70	2.09	0.77	0.92	0.42
Number of manic/hypomanic episodes	4.38	1.07	3.59	0.36	2.92	0.18	1.36	0.1933	0.58	0.1689
Length of mania	6.40	4.56	15.82	4.33	15.03	2.88	0.55	0.09	1.42	0.53
Number of mixed episodes	6.28	1.93	4.56	0.56	3.75	0.29	2.36	0.1904	0.40	0.5086
Length of mixed episodes	0.00	0.00	17.61	6.22	13.27	4.46	N/A	N/A	2.19	0.47
Suicidal ideation	40.44	7.84	34.37	4.35	27.36	2.30	1.71	0.86	1.30	0.77
Treatment (since Wave 1)										
Sought any treatment for depression	75.14	8.20	55.03	4.99	64.31	2.90	2.58	1.02	6.52	1.00
Counselor for depression	65.56	8.79	47.37	5.04	55.08	3.04	2.32	1.02	5.27	1.05
Hospitalized for depression	33.57	8.84	9.29	3.65	12.60	1.84	3.27	1.31	8.13	0.66
Emergency room for depression	30.25	8.66	9.40	3.44	14.35	2.28	2.46	1.00	6.08	0.59
Medication for depression	59.87	9.03	48.28	5.20	56.31	3.00	1.89	0.79	4.52	1.15
Sought any treatment for mania/hypomania	38.45	9.98	42.22	5.62	48.79	3.86	1.10	0.38	3.14	1.15
Counselor for mania/hypomania	26.75	9.41	33.85	5.33	40.70	3.89	1.04	0.32	3.37	1.25
Hospitalized for mania/hypomania	7.44	6.00	9.64	4.35	6.90	1.57	1.52	0.26	8.81	1.76

	Childhood <13 years old		Adolescence 13-18 years old		Adulthood 19+ years old		Childhood vs. Adulthood(ref)		Adolescence vs. Adulthood(ref)	
	MEAN or %	SE	MEAN or %	SE	MEAN or %	SE	AOR/ *	CI/p-value *	AOR/ *	CI/p-value *
Clinical Characteristics (since Wave 1)										
Emergency room for mania/hypomania	6.13	5.89	6.19	2.42	8.44	2.51	0.49	0.05	0.54	0.15
Medication for mania/hypomania	28.70	9.40	34.40	5.74	40.04	3.51	1.15	0.38	1.26	0.67
										2.40

* Adjusted for age, gender, race and income

Table 3
online. Onset of new Psychiatric Comorbidities and Functioning among individuals with Bipolar Disorders by Age at Onset Bipolar Disorder

	Childhood <13 years old		Adolescence 13-18 years old		Adulthood 19+ years old		Childhood vs. Adulthood(ref)		Adolescence vs. Adulthood(ref)	
	MEAN or %	SE	MEAN or %	SE	MEAN or %	SE	AOR/ *	CI/p-value *	AOR/ *	CI/p-value *
Onset of new Psychiatric Comorbidities (since Wave 1)										
New onset Anxiety Disorders (excluding Specific Phobia and PTSD)	23.06	6.15	25.93	2.79	27.00	2.19	1.01	0.50	1.18	0.77
New onset Substance Use Disorder (drug/alcohol abuse/dependence)	28.74	6.60	34.63	4.19	22.43	2.33	0.71	0.32	1.01	0.59
New Alcohol Abuse or Dependence	19.14	5.69	25.41	3.75	13.41	1.61	0.71	0.29	1.19	0.67
New Drug Abuse or Dependence	9.61	3.38	10.47	2.12	6.63	1.12	0.87	0.36	0.80	0.41
New Nicotine Dependence	10.33	4.39	10.12	2.68	5.79	1.24	1.39	0.45	1.47	0.59
Short-Form 12 norm-based functioning scores (Wave 2)										
Mental Component Summary	44.04	1.65	46.01	0.69	44.95	0.53	-1.32	0.4338	0.90	0.3564
Social Functioning	47.06	1.43	47.94	0.64	45.75	0.52	-0.18	0.9060	0.95	0.2891
Role of Emotional	43.92	1.66	45.74	0.68	44.25	0.52	-2.25	0.1630	-0.20	0.8224
Mental Health	45.16	1.44	46.43	0.75	45.51	0.50	-0.93	0.5412	0.60	0.5550

* Adjusted for age, gender, race and income