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Initiation of stimulant and antidepressant medication and clinical presentation in juvenile bipolar I disorder

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Abstract

Objectives—The primary purpose of this study was to examine the extent to which the initiation of stimulant and antidepressant medication was associated with the subsequent onset of juvenile bipolar I disorder (BP I). Another aim was to investigate differences in clinical presentation between youths prescribed stimulant or antidepressant medication before and after the onset of juvenile BP I disorder.

Methods—Youths between the ages of 5 and 17 years meeting full, unmodified DSM-IV diagnostic symptom criteria for BP were included in this study. Data regarding the age of onset of BP I, psychiatric comorbidities, and current symptoms of mania and depression were obtained. Medication history was recorded as part of the assessment interview with parents and youths.

Results—Of the 245 youths with BP I, 65% (n = 160) were treated with stimulant medication; 32% (56/173) were treated after the onset of BP I, and 19% (32/173) were treated before the onset of BP I. Forty-six percent (113/245) were treated with antidepressant medication; 33% (67/206) were treated after the onset of BP I, and 3% (7/206) were treated before the onset of BP I. Patients who were treated with stimulants after the onset or BP I were significantly more likely to be younger ($p < 0.0001$). Patients who were treated with antidepressants before the onset of BP I were significantly more likely to be older and to have lower levels of mania on the Young Mania Rating Scale at assessment ($p < 0.01$)

Conclusions—Data from this retrospective case series do not support the association between initial stimulant or antidepressant use and the onset of BP I or presenting symptoms of depression or manic symptoms.

Keywords

adolescents; antidepressants; bipolar disorder; children; stimulants

Pediatric bipolarity is a debilitating, chronic disorder that impairs afflicted youths' developmental and emotional growth. Furthermore, pediatric bipolar disorder has been associated with high rates of suicide, school failure, aggression, and risk-taking behaviors such as sexual promiscuity and substance abuse (1,2). Often, investigators have attempted to identify risk factors that may lead to the development of bipolar disorders in children and adolescents (3,4).

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One complication in diagnosing pediatric bipolarity is that there is an overlap in symptoms of bipolar disorder (hyperactivity, dysphoria, irritability, and aggressive behavior) with other common psychiatric conditions in youths such as attention-deficit hyperactivity disorder (ADHD), depression, and conduct disorder (5–8). Juvenile bipolar disorder is commonly misdiagnosed, due to the high rates of psychiatric comorbidity, high rates of rapid cycling without inter-episode recovery, and brief periods of euthymia (9). These challenges in combination with changes in diagnostic practices to improve recognition of bipolar I disorder (BP I) may contribute to the varying rates of BP I among youths in community, epidemiological, and pediatric research centers. Given the lack of knowledge of the phenomenology, course, or symptomatic evolution of BP I, it is not surprising that some youths with BP I are treated with stimulants or antidepressants.

Concerns have been raised about the effects of stimulant and antidepressant treatment in children with BP I (10,11). One theory is that prior stimulant and antidepressant exposure may put youths at higher risk for developing bipolar disorder (12–14). More specifically, the higher rate of BP I in the United States may be related to the greater use of antidepressants and stimulants by US children (13).

The aim of this study is twofold: (i) to examine the initiation of antidepressant and stimulant treatment in relation to the onset of BP I; and (ii) to examine the clinical presentation of youths prescribed stimulant and antidepressant medication before and after the onset of BP I.

Methods

Subjects

Potential subjects were recruited for this protocol from research patients seen at a clinical research center (CRC) located within an urban, university-based, division of child and adolescent psychiatry. The CRC is dedicated to the study of juvenile bipolar disorders. The participants for this study were recruited as part of the screening procedures for various treatment CRC studies.

Eligible subjects were between the ages of 5 and 17 years (inclusive). Patients with a diagnosed or suspected pervasive developmental disorder, a psychiatric disorder due to a general medical condition, or evidence of mental retardation were not enrolled (exclusive). In order for a patient to be eligible for this protocol, patients must have met full DSM-IV diagnostic criteria for a primary diagnosis of BP I.

All procedures of this study were approved by the University Hospitals of Cleveland Institutional Review Board for Human Investigation. Written informed consent and assent of parents/guardians and patients were obtained prior to participation in this study.

Diagnosis

Lifetime and current DSM-IV diagnoses were assessed based on the results of either the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic version (KSADS-E) or the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (KSADS-PL) (15). The KSADS-E was initially employed. However, because the KSADS-PL has modules that can be omitted based upon informant response, later patients in this study were interviewed with the KSADS-PL when it subsequently became available. The KSADS assessment was administered by a child and adolescent psychiatrist or by highly trained research assistants [ranging from BA in psychology to PhD or MD; for a detailed description of rater education and clinical experience, see (9)]. All research assistants were trained to reach an overall

kappa > 0.85 at the item severity level. During the KSADS interview, the research assistant recorded the age of disorder onset. To accomplish this, the research assistant first identified chronological anchor points, such as holidays, to help the parent/guardian report when the disorder occurred and the corresponding age of the child at the onset of the disorder. As part of screening procedures for clinical trials, a physician subsequently evaluated 80% of the patients with bipolar diagnoses, confirming the KSADS diagnosis and age of onset in more than 95% of cases.

For a patient to receive the diagnosis and recorded age of onset of one or more comorbid psychiatric disorders in addition to BP I, a patient needed to meet full DSM-IV diagnostic symptom criteria for each comorbid diagnosis during identified periods of neutral mood according to the semi-structured diagnostic interview.

Measures

Child Depression Rating Scale-Revised edition—The Child Depression Rating Scale-Revised edition (CDRS-R) (16) is a 17-item clinical rating scale designed to evaluate the severity of symptoms of depression. It has demonstrated good validity and psychometric properties (17,18).

Young Mania Rating Scale—The Young Mania Rating Scale (YMRS) is a clinical rating scale containing 11 items assessing manic symptoms. These are rated on a 0–4 scale, with some item scores doubled to weight for their clinical importance and low base rate (19). It has demonstrated good reliability and discriminate validity (20,21).

Medication history—Medication history of patients was ascertained as part of the assessment interview with parents and youths. During this assessment, information from parents, youths, and available medical records were reviewed. Detailed documentation regarding past and current medication treatment was recorded, including the following: dates of initiation and discontinuation, type, and daily dose. The age of the patient at first initiation of medication(s) was ascertained by one of two methods: (i) the length of time between the date of medication initiation of the first stimulant and/or antidepressant and date of birth; or (ii) age of the youth at first stimulant and/or antidepressant treatment. A minority of patients (n = 2) were prescribed multiple antidepressant medications simultaneously (bupropion in conjunction with either citalopram or fluoxetine). If information regarding the date or age of first medication initiation was not provided, these cases were not included in analyses regarding medication initiation [15% (n = 36) of data regarding antidepressants and 26% (n = 64) regarding stimulants]. There were no significant demographic or clinical differences between those with and without information regarding initiation of stimulant and/or antidepressant medication. For analyses regarding medication initiation, four medication initiation categories were constructed: disorder onset, never prescribed medication; disorder onset following being treated with medication (at least 3 months following); disorder onset at the same time of being treated with medication (±3 months of disorder onset); and disorder onset prior to being treated with medication (at least 3 months prior). The three-month window was used to allow caution about determination of chronological ordering of initiation of medication and disorder onset. It was presumed that a six-month window (± 3 months of disorder onset) was within reasonable limits of identifying youths who develop a disorder at the same time of medication initiation, as well as reduces unavoidable measurement error variance.

Statistical analyses

Nominal data were compared to the chi-squared test or Fisher's exact test using the PROC FREQ procedure, as appropriate. Continuous data were initially assessed for normal

distribution with the Lilliefors and Kolmogorov–Smirnov test. Since the majority of variables did not meet this stringent standard for normal distribution, data were analyzed using non-parametric statistics using the PROC NPAR1WAY procedure. The magnitude of parametric differences between groups was calculated for the effect size index *d*, using Cohen's categories of small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$) (22). Given the descriptive and exploratory nature of the analyses, all tests were reported with significance values >95% ($p < 0.05$), two tailed. Statistical analyses were performed by using SAS statistical software, version 9.1 (SAS Institute, Cary, NC, USA) (23).

Results

Clinical description

A total of 245 patients between the ages of 5 and 18 years [mean (SD) = 10.98 (3.49) years] who met DSM-IV criteria for BP I were enrolled in this study. Eighteen percent (n =44) were assessed using the KSADS-E and the other patients were assessed using the KSADS-PL. Demographic information about these youths can be found in Table 1. The sample was predominately male (67%) and Caucasian (81%). The average age of youths at assessment was approximately 11 years (SD = 3.93), and the average age of patients' BP I onset was 6.60 years (SD = 3.93 years). Approximately half of the sample met criteria for bipolar with rapid cycling (n = 126). Seventy-five percent (n = 183) of the sample had concurrent ADHD, and 47% (n = 115) had concurrent disruptive behavior disorder (DBD). The average age of onset was approximately 4 years for ADHD [mean (SD) = 3.77 (2.03) years], 5 years for DBD [mean (SD) = 5.26 (3.11) years], and 6 years for BP I [mean (SD) = 6.60 (3.93) years].

Over the course of their lifetime, the average total number of psychotropic medications that had been prescribed to these youths was 3.64 (SD = 3.42). At the time of assessment, the youths were prescribed an average of 1.51 (SD = 1.25) psychotropic medications. Sixty-five percent (160/245) of youths had a history of being treated with stimulant medication, and 33% (79/245) were being treated with stimulant medication at assessment (Table 2). Table 2 also presents information regarding the first stimulant use among those with parent knowledge of the date of first stimulant initiation (n = 96). The average age of first stimulant treatment was 7.06 years (SD = 3.09 years), with an average length of treatment of two years [mean (SD) = 1.96(2.12) years]. Methylphenidate-based preparations (83%) were the most common initial stimulants prescribed.

As shown in Table 2, 46% (113/245) of BP I youths had a history of being treated with antidepressant medication, and 16% (39/245) were being treated with antidepressant medication at assessment. Table 2 also presents information regarding the first antidepressant use among those with parent knowledge of the date of first antidepressant initiation (n = 77). The average age of first antidepressant use was 9.52 years (SD = 3.26 years), with an average length of treatment approaching one year [mean (SD) = 0.86 (1.31) years]. Selective serotonin reuptake inhibitor [(SSRI) 64%] was the most common type of initial antidepressant prescribed.

Medication history in relation to comorbid diagnosis

Youths with BP I and comorbid ADHD or DBD were significantly more likely to be currently treated or have been treated with stimulant medication. Youths with BP I and comorbid ADHD were significantly more likely to currently be taking stimulants in comparison to those without ADHD (43% versus 5%; $\chi^2 = 29.87$, df = 1, $p < 0.0001$, $d = 0.35$), as well as have a past history of stimulant treatment (79% versus 26%; $\chi^2 = 57.16$, df = l, $p < 0.0001$, $d = 0.48$). Patients with comorbid DBD were significantly more likely to

currently be taking stimulants in comparison to those without DBD (41% versus 26%; χ^2 = 5.97, df = l, p = 0.015, *d* = 0.16), as well as have a past history of stimulant treatment (73% versus 58%; χ^2 = 5.73, df= 1, p = 0.017, *d*= 0.15).

Few differences emerged with regard to current or past history of antidepressant medication and the presence of ADHD or DBD. Youths with BP I and comorbid ADHD had similar rates of current antidepressant treatment (16% versus 15%; not significant), as well as past antidepressant treatment (45% versus 50%; not significant). Patients with comorbid DBD had similar rates of current antidepressant treatment (19% versus 13%; not significant), but had significantly higher rates of past antidepressant treatment (54% versus 39%; χ^2 = 5.29, df = l, p = 0.021, *d*= 0.15).

Medication initiation and clinical presentation

The clinical presentation of youths who were treated with stimulants before or after BP I onset, or never treated, was examined for those with parent knowledge of date of initial stimulant use. Because so few youths started taking stimulant medication at the same time as the BP I onset (n = 2), this classification group was not included in comparisons, resulting in a sample of 179 youths for initial stimulant comparisons in relation to onset of BP I. As shown in Table 3, age of onset of BP I was significantly associated with onset of stimulant medication classification groups [never, prior, and post (Kruskal–Wallis test; χ^2 = 31.65; p < 0.0001)]. The youths who initiated stimulant medication following the onset of BP I were significantly younger [mean (SD) = 4.52 (2.74) years] than those who initiated stimulant medication prior to BP I onset [mean (SD) = 6.20 (3,53) years] or never received stimulant medication [mean (SD) = 5.63 (3.53) years]. No significant differences were found between initial stimulant treatment relative to BP I onset and the age of ADHD onset, age of DBD onset, history of psychiatric hospitalization, bipolar with rapid cycling, CDRS-R scores, or YMRS scores.

With regard to antidepressant initiation, a different pattern emerged (Table 4). Because so few youths started taking antidepressant medication at the same time as the BP I onset (n = 3), this classification group was not included in comparisons, resulting in 206 youths with parent knowledge of date of initial antidepressant use. At assessment, youths who initiated antidepressant medication prior to the onset of BP I were significantly older [mean (SD) = 10.64 (4.11) years] than those who initiated antidepressant medication following BP I onset [mean (SD) = 6.12 (3.69) years] or never received antidepressant medication [mean (SD) = 6.25 (3,69) years; Kruskal–Wallis test; χ^2 = 7.27; p = 0.03].

Youths who started antidepressant treatment prior to BP I onset had significantly lower YMRS scores in comparison to the other groups (Kruskal–Wallis test; χ^2 = 6.74; p = 0.03). Youths prescribed antidepressants following the onset of BP I had significantly elevated CDRS-R scores in comparison to those who were never prescribed antidepressants (Kruskal–Wallis test; χ^2 = 9.54; p = 0.008), but no differences emerged compared to youths prescribed antidepressants prior to BP I onset. There were no significant differences between initial antidepressant treatment relative to BP I onset and the age of ADHD onset, age of DBD onset, and rate of bipolar disorder with rapid cycling.

Discussion

Results from this study are among the first to describe a historical perspective of the onset of illness and medication initiation in juveniles with BP I. Although other studies have raised concern about the risk of developing BP I following prior exposure to stimulant and antidepressant medication (12–14,24), our study aligns with those who have not found adverse effects in children with or at risk for developing BP I (25—27). The present study

has several methodological strengths that further knowledge about BP I in children and adolescents. The sample size is one of the largest of juveniles with bipolar illness and has a greater age span at which to examine the phenomenology of this disorder. The naturalistic design of this study offers a real-world perspective in terms of clinical presentation, psychiatric comorbidity, and medication patterns of youths with BP I in clinical populations. With multiple methods of assessment that provide validity of psychiatric diagnoses and detailed information regarding medication treatment history, this study offers a unique opportunity to evaluate the possible causal link between medication and psychiatric disorder development.

The high rates of comorbid ADHD and DBD are similar to those found in other studies of bipolar youths (28,29). Approximately two-thirds of youths with BP I had past stimulant treatment, and one-third were currently receiving stimulant treatment. The most common psychostimulant prescribed was methylphenidate (83%), a rate nearly identical to the 82% rate found in other clinical samples (12). Almost half of the sample had a prior history of antidepressant treatment; approximately one-sixth of youths with BP I were currently receiving antidepressant treatment, the most common type of which was SSRI. Patients with a comorbid diagnosis (either ADHD or DBD) were significantly more likely to report current and past stimulant treatment, which suggests the recognition and treatment of these disorders. More than half of BP I youths with comorbid conditions were not currently receiving any psychotropic medications.

To investigate the potentially causal relationship between medication treatment and the development of BP I, rates at which BP I onset occurred before, at the same time as, or after initiation of medication was examined. In this representative sample, approximately one-fifth of youths were treated with psychostimulants prior to the onset of BP I. Only 3% of youths were treated with antidepressant medication prior to the onset of BP I. Thus, for the majority of youths with BP I, the prescription of these agents did not precede the onset of BP I.

Several interesting findings emerged with regard to age at BP I onset and initiation of psychostimulant and antidepressant medication. Youths who initiated stimulant medication therapy following the onset of BP I were significantly younger in age compared to those who initiated stimulant medication prior to BP I onset, or never received stimulant medication. Youths prescribed antidepressants prior to BP I onset were the oldest patients with BP I. Thus, these results do not appear to support the hypothesis of earlier onset of BP I in children by antidepressants or stimulants (13,24).

The methodological strengths of this study address several design limitations of prior work, which may explain why these findings may differ from others. It is also possible that recognition of BP I has improved such that children are being identified at younger ages and subsequently treated with medication. Causation of earlier onset of BP I in children by antidepressants or stimulants requires careful consideration of which came first — the stimulant treatment or the onset of BP I.

Are clinical characteristics worse among patients who take stimulant or antidepressant medication prior to BP I onset? This study was sufficiently large enough to detect medium to large effects, yet no clinical differences were found between patients pre- and post-stimulant initiation in rates of BP I with rapid cycling, age of ADHD or DBD onset, CDRS-R scores, or YMRS scores. The same pattern was found with regard to antidepressant initiation and clinical outcomes, with the exception of YMRS scores: lower YMRS scores were found in youths prescribed antidepressant medication prior to BP I onset. This suggests

that prior use of antidepressants does not appear to lead to higher levels of mania in patients with BP I.

There are several limitations that need to be considered when interpreting the results of the study. First, historical timeline methods were employed to identify the age at onset of BP I, whereas the optimal method for ascertainment of age of onset of BP I is through hospitalization or medical records. Second, parents who report the age of BP I onset among their children at very young ages pose methodological challenges. In our study, a small proportion of parents retrospectively identified the age of BP I onset at age three years or younger [the mean (SD) age at intake for these youths was 9.16 (2.81) years]. For subjects with a very young age of BP I onset, the KSADS diagnosis and age of onset were confirmed by physician evaluation in 100% of cases (n = 36). However, the validity of age of BP I onset among very young children is an area for future research that would greatly benefit from prospective assessments with parents. The third limitation pertains to reports of initial medication use. Ascertainment of initial medication use was retrospective for a portion of the sample whose first trial was not at the time of the assessment. In addition, medication history was not verified by a medical chart review. Studies employing medical chart review for age of disorder onset and medication history are needed to replicate study findings. Finally, a substantial number of parents were not able to provide an initial date of medication use. However, these subjects did not differ on demographic or clinical variables to those with initial dates, and results remained significant when using the method of extreme case application of missing data (30). It should be noted that missing data applications cannot substitute for actual dates of medication initiation and how this data may influence outcomes. Prospective studies that examine the relationship between medication initiation and BP I onset are needed in order to confirm or refute these results.

In summary, this study does not document an association with initial stimulant or antidepressant medication and BP I onset, or presenting symptoms of depression or manic symptoms. However, the need for careful assessment and clinical monitoring during psychostimulant and antidepressant treatment cannot be overemphasized. Future investigations, such as the NIMH-sponsored Longitudinal Assessment of Manic Symptoms, will provide the necessary, prospective examination of initiation of these agents in relation to the age at onset of BP I, as well as new onsets or recurrences of comorbid disorders. All subjects in this study had BP I; future investigations are needed to prospectively examine whether stimulant or antidepressant medications promote the onset of BP I among youths who are at-risk for developing this disorder.

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Table 1

Demographic characteristics and selected current comorbidities in a sample of youths with bipolar I disorder

Total, n (%)	245 (100)
Gender, n (%)	
Male	161 (66)
Female	84 (34)
Ethnicity, n (%)	
Native American	1 (6)
Black	20 (8)
Hispanic	10 (4)
White	199 (81)
Other	15 (6)
Age (years), mean (SD)	10.93 (3.49)
Bipolar I age of onset (years), mean (SD)	6.60 (3.93)
Bipolar I with rapid cycling, n (%)	126 (51)
Comorbid ADHD, n (%)	
ADHD combined type	157 (64)
ADHD inattentive type	17 (7)
ADHD hyperactive type	4 (2)
ADHD NOS	5 (2)
Any	183 (75)
ADHD age of onset (years), mean (SD)[a]	3.77 (2.03)
Comorbid DBD, n (%)	
Conduct disorder	44 (18)
Oppositional defiant	100 (41)
Any	115 (47)
DBD age of onset (years), mean (SD)[a]	5.26(3.11)

ADHD = attention-deficit hyperactivity disorder; NOS = not otherwise specified; DBD = disruptive behavior disorder.

[a]For subjects with more than one current comorbid condition in one of the three delineated classes of disorders listed above, the age of onset at which the first disorder appeared in that class of disorders is referenced.

Table 2

Medication characteristics of youths with bipolar I disorder

Medication characteristic, n (%)	245 (100)
Ever stimulant, n (%)	
NO	85 (35)
Yes	160 (65)
First stimulant medication received[a], n (%)	96 (100)
Type, n (%)	
Methylphenidate-based	80 (83)
Amphetamine-based	15 (16)
Pemoiine	1 (1)
Stimulant treatment length (years), mean (SD)	1.94 (2.12)
Age of starting first stimulant (years), mean (SD)	7.06 (3.09)
Ever antidepressant, n (%)	
No	132 (54)
Yes	113 (46)
First antidepressant medication received[a,b], n (%)	77 (100)
Type, n (%)	
Tri cyclic	13 (17)
Selective serotonin reuptake inhibitor	49 (64)
Other antidepressant	17 (22)
Antidepressant treatment length (years), mean (SD)	0.82 (1.31)
Age of starting first antidepressant (years), mean (SD)	9.52 (3.26)

[a] Medication characteristics reported for those with parent knowledge of date of medication initiation.

[b] Percents total more than 100% due to the few subjects taking multiple medications within the same class.

Table 3

Ordering of bipolar I (IBP I)/stimulant use in relation to youths' clinical presentation

		Timing of stimulant use in relation to BP I onset[ab]		
	Total	**Never Med**	**Before BP**	**Post BP**
Clinical presentation, n (%)	173 (100)	85 (49)	32 (19)	56 (32)
Age of onset (years): BP I, mean (SD)	6.93 (4.14)	7.72 (4.43)[2]	9.06 (3 43)[2]	4.52 (2.74)[1]
Age of onset (years): DBD. mean (SD)	5.53 (3.14)	5.63 (3.61)	6.20 (3.53)	5.07 (2.36)
Age of onset (years): ADHD, mean (SD)	3.72 (1.96)	3.46 (1.75)	3.76 (1.57)	3.88 (2.32)
Bipolar with rapid cycling, n (%)				
No	91 (53)	44 (52)	19 (59)	28 (50)
Yes	82 (47)	41 (48)	13 (41)	28 (50)
CDRS-R, mean (SD)	33.05 (14.17)	34.34 (14.10)	32.96 (14.56)	31.10 (14.12)
YMRS, mean (SD)	25.08 (8.67)	24.25 (8 22)	25.00 (10.36)	26.40 (8.34)

DBD = disruptive behavior disorder; ADHD = attention-deficit hyperactivity disorder; CDRS-R = Child Depression Rating Scale-Revised edition; YMRS = Young Mania Rating Scale.

[a] Analyses conducted among those with parent knowledge of date of medication initiation.

[b] Superscript numbers that are different from others are significantly different, $p < 0.0001$.

Table 4

Ordering of bipolar I (BP I)/antidepressant use in relation to youths' clinical presentation

		Timing of antidepressant use in relation to BP I onset[a,b]		
	Total	**Never Med**	**Before BP**	**Post BP**
Clinical presentation, n (%)	206 (100)	132 (64)	7 (3)	67 (33)
Age of onset (years): BP I, mean (SD)	6 36 (3.77)	6.25 (3.69)[2]	10.64 (4.11)[1]	6.12 (3.69)[2]
Age of onset (years): DBD, mean (SD)	5.16 (2.94)	5.04 (2.93)	7.67 (6.43)	5.11 (2.59)
Age of onset (years): ADHD, mean (SD)	3.75 (1.98)	3.74 (2.01)	3.60 (2.70)	3.78 (1.91)
Bipolar with rapid cycling, n (%)				
No	104 (50)	70 (53)	5 (71)	29 (43)
Yes	102 (50)	62 (47)	2 (29)	38 (57)
CDRS-R, mean (SD)	32.56 (14.13)	29.99 (12.31)[1]	36.20 (7.95)[2]	38.00 (16.75)[2]
YMRS, mean (SD)	25.06 (8.59)	24.73 (8.69)[2]	14.60 (13.56)[1]	26.78 (7.10)[2]

DBD = disruptive behavior disorder; ADHD = attention-deficit hyperactivity disorder; CDRS-R = Child Depression Rating Scale-Revised edition; YMRS = Young Mania Rating Scale.

[a] Analyses conducted among those with parent knowledge of date of medication initiation.

[b] Superscript numbers that are different from others are significantly different, $p < 0.01$.