Bipolar Disorders 2001: 3: 53–57
Printed in Ireland. All rights reserved

BIPOLAR DISORDERS
ISSN 1398-5647

Brief Report

Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset

DelBello MP, Soutullo CA, Hendricks W, Niemeier RT, McElroy SL, Strakowski SM. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset.
Bipolar Disord 2001: 3: 53–57. © Munksguaard, 2001

Objectives: To compare demographic and clinical characteristics between bipolar adolescents with and without a history of stimulant treatment, we hypothesized that adolescents treated with stimulants would have an earlier age at onset of bipolar disorder, independent of co-occurring attention-deficit-hyperactivity disorder (ADHD).

Method: Thirty-four adolescents hospitalized with mania were assessed using the Washington University at St Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS). We systematically evaluated age at onset of bipolar disorder and pharmacological treatment history.

Results: Bipolar adolescents with a history of stimulant exposure prior to the onset of bipolar disorder had an earlier age at onset of bipolar disorder than those without prior stimulant exposure. Additionally, bipolar adolescents treated with at least two stimulant medications had a younger age at onset compared with those who were treated with one stimulant. There was no difference in age at onset of bipolar disorder between bipolar adolescents with and without ADHD.

Conclusions: Our results suggest that stimulant treatment, independent of ADHD, is associated with younger age at onset of bipolar disorder. A behavioral sensitization model is proposed to explain our findings. There are several limitations to our study including the small sample size, the retrospective assessment of stimulant exposure and age at onset of bipolar disorder, and the inclusion of only hospitalized patients, who may be more likely to present with a severe illness. Nonetheless, future prospective longitudinal investigations that systematically assess the effects of stimulant medications in children with or at genetic risk for bipolar disorder are warranted.

Melissa P DelBello, Cesar A Soutullo, Wendi Hendricks, R Todd Niemeier, Susan L McElroy and Stephen M Strakowski

From the Bipolar and Psychotic Disorders Research and Biological Psychiatry Programs, Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH

Key words: adolescents – attention-deficit-hyperactivity disorder – bipolar disorder – stimulants

Received 11 September 2000, revised and accepted for publication 20 December 2000

Corresponding author: Melissa P DelBello, MD, Department of Psychiatry, University of Cincinnati College of Medicine, 231 Bethesda Ave., PO Box 670559, Cincinnati, OH 45267-0559, USA. Tel: +1 513-558-0956; fax: +1 513-558-3399; e-mail: delbelmp@email.uc.edu

Despite the high co-occurrence of juvenile mania and attention-deficit-hyperactivity disorder (ADHD), the relationship between these disorders remains unclear (1–7). Explanations for this high co-morbidity include juvenile mania with ADHD being a distinct form of early-onset bipolar disorder (3), ADHD being a prodrome of juvenile mania, or simply a misclassification because of symptom overlap between the two conditions (5). Nonetheless, because of the high rate of co-occurrence of these disorders and the perceived confusion in differentiating their clinical presentations, children with bipolar disorder are often initially treated with stimulants prior to the onset of their illness or early in its course (8).

Although stimulant medications generally do not have long-term adverse effects in non-bipolar children with ADHD, the consequences of stimulant exposure in children with or at risk for developing bipolar disorder are less clear (9–11). Despite a few reports suggesting the effectiveness of stimulants in the short-term treatment of mania

(12, 13), several case reports indicate that these agents may worsen the symptoms of bipolar disorder (14, 15). Furthermore, we previously reported in a retrospective chart review, that stimulant-exposed bipolar adolescents had an overall worse hospital course as compared with non-exposed bipolar adolescents (16). Moreover, children with bipolar disorder and ADHD do not respond to lithium as well as bipolar children without ADHD, suggesting that the co-occurrence of ADHD may lead to a poorer response to mood stabilizers. However, in this study prior treatment with stimulants was not reported and it is possible that chronic stimulant exposure may exacerbate the course of bipolar disorder (17).

Increased dopaminergic neurotransmission may contribute to the neuropathophysiology of mania (18). Therefore, chronic stimulant exposure in children who have an underlying risk for bipolar disorder may lead to an earlier age at onset by precipitating affective episodes. With these considerations in mind, the aim of our study was to compare demographic and clinical characteristics between bipolar adolescents hospitalized for mania with and without a history of stimulant treatment prior to the onset of bipolar disorder. We hypothesized that adolescents treated with stimulants would have an earlier age at onset of bipolar disorder, independent of co-occurring ADHD.

Methods

Thirty-four adolescents (ages 12–19 years), hospitalized with mania, were recruited from consecutive admissions to the Adolescent Psychiatry Unit at Cincinnati Children's Hospital Medical Center, composed of two 12-bed units that serve the psychiatric needs of adolescents from southeastern Indiana, northern Kentucky, and southwestern Ohio. Patients were included if: a) they were 12–19 years old, b) they met DSM-IV criteria for bipolar disorder manic or mixed, and c) they or a legal guardian (if aged less than 18 years) provided written informed consent. Patients were excluded if: a) their symptoms resulted entirely from acute intoxication or withdrawal from drugs or alcohol as determined by medical evaluation, a positive toxicology screening, and rapid symptom resolution within 72 h of admission; or b) they had a history of mental retardation (i.e. IQ < 70) (19).

DSM-IV axis I diagnoses were made using the Washington University at St Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (20, 21) administered by trained raters with good diagnostic and symptom reliability (kappa $= 0.94$) who were blind to prior treatment status. Adolescents and their parents were interviewed separately and diagnoses were reviewed at a consensus conference attended by a least one child and adolescent psychiatrist (M.P.D., C.A.S.). Previous and current medications were systematically assessed by interviewing the adolescents and their parents, and when available, reviewing medical records. Specifically, adolescents and their parents were asked about the duration of treatment with each stimulant medication (dextroamphetamine, methylphenidate, and adderall®). None of the adolescents took stimulants that were not prescribed by a physician. Additionally, all of the adolescents were prescribed stimulants for inattention, hyperactivity, and/or impulsivity. Medical records were obtained for verification when necessary. Age at onset for bipolar disorder 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; kappa $= 0.94$) (22). Alcohol and other drug abuse and dependence were classified as 'substance use disorders'. All adolescents were Tanner stage IV or V (23).

Statistical analysis

Non-parametric statistical analyses were performed using Statistical Analysis System (SAS Institute, Cary, NC). The demographics and clinical variables between bipolar adolescents with and without stimulant treatment were compared using Wilcoxon rank-sums and Fisher's exact tests. An analysis of co-variance (ANCOVA), adjusting for variables that significantly differed between the groups (current age and ADHD), was used to compare age at onset of bipolar disorder between adolescents with and without stimulant treatment. Other statistical analyses were completed as necessary.

Results

Twenty-one of the 34 (62%) bipolar adolescents had treatment with at least one stimulant medication for greater than 1 week. There was no statistically significant difference in race, sex, or rates of mixed states, oppositional defiant disorder (ODD), conduct disorder (CD), or substance use disorders between bipolar adolescents with and without a history of stimulant treatment (Table 1). The mean age of onset of bipolar disorder was 11.9 ± 4.1 years (range 5.0–18.0). Adolescents who were diagnosed with substance use disorders abused alcohol and marijuana. Three of the eight (38%) bipolar adolescents diagnosed with substance use disorders had been treated with stimulants.

Bipolar adolescents with stimulant exposure ($n = 21$) were more likely to have co-occurring ADHD (Fisher's exact test, $p = 0.02$) compared with those without a history of stimulant treatment ($n = 13$). Bipolar adolescents with a history of stimulant treatment were non-significantly younger ($Z = 1.8$, $df = 1$, $p = 0.07$) than those without stimulant treatment. Bipolar adolescents with a history of stimulant exposure had an earlier age at onset of bipolar disorder than those without prior stimulant exposure (10.7 ± 3.9, range 5.0–15.0 years vs. 13.9 ± 3.7, range 8.0–18.0 years, $Z = 2.3$, $df = 1$, $p = 0.01$), even after adjusting for current age and presence of ADHD [$F(1,33) = 5.1$, $p = 0.03$].

All of the adolescents with a history of stimulant treatment were initially treated with stimulants prior to the onset of an affective episode. Mean duration of stimulant treatment was 48 ± 35 months. Four (19%) adolescents were treated with stimulants for less than 1 year and nine (43%) adolescents were treated with stimulants for more than 5 years. At the time of evaluation 10 patients were being treated with stimulants (48%). There was no significant correlation between age at onset of bipolar disorder and duration of stimulant treatment (Spearman rank coefficient, $r = 0.03$, $p = 0.9$).

The majority of bipolar adolescents who were treated with stimulants ($n = 18$, 82%) were prescribed methylphenidate. Nine (50%) of the adolescents who were treated with methylphenidate were also prescribed either dextroamphetamine, Adderall, and/or pemoline at some point prior to the onset of bipolar disorder (not concurrently with methylphenidate). Three (18%) of the adolescents who were treated with stimulants were only exposed to dextroamphetamine. There was no statistically significant difference in current age, race, sex, duration of stimulant exposure, or rates of mixed episodes, ADHD, ODD, CD, or substance use disorders between bipolar adolescents treated with methylphenidate and those treated with methylphenidate and dextroamphetamine, Adderall, and/or pemoline. However, bipolar adolescents treated with at least two stimulant medications ($n = 9$) had a younger age at onset of bipolar disorder compared with those who were treated with only methylphenidate ($n = 9$, 8.9 ± 4.6 vs. 12.7 ± 2.1 years, $Z = 1.7$, $df = 1$, $p = 0.04$).

There was no statistically significant difference in current age, race, sex, duration of stimulant exposure, or rates of mixed episodes, ADHD, ODD, CD, or substance use disorders between bipolar adolescents treated with only one stimulant medication and those treated with more than one stimulant medication. There was a statistical trend for bipolar adolescents who were exposed to at least two stimulant medications ($n = 9$) to have a younger age at onset of bipolar disorder than those exposed to only one stimulant medication ($n = 12$, 8.9 ± 4.6 vs. 12.0 ± 2.8 years, $Z = -1.4$, $df = 1$, $p = 0.07$).

There was no statistically significant difference in age, sex, race, rates of mixed episodes, or age at onset of bipolar disorder between bipolar adolescents with ($n = 22$) and without ADHD ($n = 12$). Age of onset of bipolar disorder was 11.7 ± 4.0 in the adolescents without ADHD and 12.0 ± 4.2 in the adolescents with ADHD ($Z = -0.5$, $df = 1$, $p = 0.6$). Bipolar adolescents with ADHD were more likely to have ODD (59% vs. 17%, Fisher's exact test, $p = 0.03$) and CD (45% vs. 8%, Fisher's exact test, $p = 0.05$) as compared to those without ADHD. Within the group of bipolar adolescents with ADHD ($n = 22$), those with a history of stimulant treatment ($n = 17$) had a younger age of onset of bipolar disorder as compared with those without prior stimulant exposure ($n = 5$, 10.8 ± 4.0 vs. 16.0 ± 1.9 years, $Z = 2.8$, $df = 1$, $p = 0.002$).

Table 1. Comparison of demographic and clinical characteristics of bipolar adolescents with and without stimulant treatment

	Stimulants (n = 21)	No stimulants (n = 13)
Age, mean (SD) years	15.1 (1.7)	16.4 (2.0)
Sex, n (%) female	5 (24)	4 (31)
Race, n (%) African American	3 (14)	4 (19)
Currently manic (versus mixed), n (%)	5 (24)	5 (38)
ADHD, n (%)[a]	17 (81)	5 (38)
CD, n (%)	9 (43)	2 (15)
ODD, n (%)	10 (48)	5 (38)
Substance use disorders, n (%)	3 (14)	5 (38)
Age at onset of bipolar disorder, mean (SD) years[b]	10.7 (3.9)	13.9 (3.7)

[a]Fisher's exact test, $p = 0.02$.
[b]ANCOVA: $F(1,33) = 5.1$, $p = 0.03$.
ADHD = attention-deficit-hyperactivity disorder; CD = conduct disorder; ODD = oppositional defiant disorder

Discussion

The high rates of co-morbid ADHD, CD, and ODD found in our study are similar to those found in other studies of bipolar adolescents (1–3, 6, 7, 15). Supporting our hypothesis, bipolar adolescents with stimulant exposure, particularly those exposed to more than one stimulant, had a younger age at onset of bipolar disorder than those

without a history of stimulant exposure. However, bipolar adolescents with and without ADHD had similar ages of onset, suggesting stimulant exposure and not ADHD may lead to an earlier onset of bipolar disorder in children and adolescents. Alternatively, bipolar children may have prodromal or subsyndromal symptomatology other than syndromal ADHD. Therefore, the younger age at onset of bipolar disorder in adolescents with a history of stimulant treatment may be because of a more severe illness presentation for which they are prescribed stimulant medications. Additionally, we found that bipolar adolescents treated with more than one stimulant medication have a younger age at onset, suggesting that different stimulants with varying mechanisms of action may act synergistically to precipitate affective symptomatology in children who develop bipolar disorder. Our results indicate no correlation between age at onset and duration of stimulant exposure. This may be because of the limited variability in duration of stimulant exposure in our sample (most adolescents were treated with stimulants for at least 2 years). Perhaps, there is a threshold of exposure, which most of the adolescents in our study surpassed, after which affective symptoms manifest. Prospective studies are necessary to clarify the effects of stimulant medications in children with or at risk for developing bipolar disorder as well as, to determine whether stimulants precipitate depression and/or mania in children who would not have otherwise developed bipolar disorder or hasten the onset in those who are destined to develop the illness.

To our knowledge, there has been one controlled prospective study examining treatment with methylphenidate monotherapy, lithium monotherapy, and lithium and methylphenidate in combination in children diagnosed with major depression or bipolar symptoms and a disruptive behavioral disorder ($n = 7$) (11). The study measured inattention and hyperactivity/overactivity symptoms over the course of treatment and found attention was improved on lithium and methylphenidate combined therapy. However, no significant medication effect was found for the overactivity ratings. This study suggests that neither lithium nor methylphenidate alone ameliorated or exacerbated hyperactivity or inattention in children with mood symptoms and disruptive behavioral disorders. However, this study did not examine mood symptoms over the course of treatment and although duration of exposure to methylphenidate was not exactly quantified, it was relatively short (weeks as opposed to months). Therefore, this study did not address the long-term effects of methylphenidate treatment on mood regulation in children.

In a more recent study El-Mallakh reported the effectiveness of open-label methylphenidate in the treatment of bipolar depression. This study examined the acute (12 weeks) effects of methylphenidate as adjunctive treatment to mood stabilizers and did not examine the long-term effects of treatment with methylphenidate, without a concomitant mood stabilizer (24).

The exact mechanism by which stimulants might influence the course of juvenile bipolar disorder remains unknown. However, behavioral sensitization provides one model to explain our findings, as well as observations of stimulant-induced mania. Behavioral sensitization is the process by which intermittent, stressful stimuli produce an enduring and progressively more robust response (25, 26). Stimulant exposure may be a stressor in children and adolescents with or who are at genetic risk for developing bipolar disorder and may, therefore, lead to a progressive worsening of affective symptoms over time. Thus, a behavioral sensitization model of bipolar disorder would predict that prior to the onset of bipolar disorder, children with the predisposition for developing this illness will exhibit increased frequency, severity, and duration of their affective symptoms when treated with stimulants; and, consistent with our data, these children may develop bipolar disorder at a younger age.

There are several limitations to our study including the small sample size, the retrospective assessment of stimulant exposure and age at onset of bipolar disorder, and the inclusion of only hospitalized patients, who may be more likely to present with a severe illness. Additionally, family history data would be useful in future studies to evaluate whether bipolar adolescents with a history of stimulant treatment and a younger age at onset are more likely to have a genetic risk for developing the illness. Future studies should also examine age of stimulant exposure and subsequent time to first affective or manic episode. Although there are limitations to our study, the results have significant clinical implications. Our findings raise the importance of the need for carefully evaluating affective symptomatology in children prior to treatment with stimulant medications. Moreover, our data suggest that future prospective longitudinal investigations that systematically assess the effects of stimulant medications in children with or at genetic risk for bipolar disorder are warranted.

Acknowledgements

NIMH grant MH54317 (SS) and the Theodore and Vada Stanley Foundation.

References

1. Beiderman J, Faraone S, Mick E et al. Attention-deficit hyperactivity disorder and juvenile mania: a overlooked comorbidity? J Am Acad Child Adolec Psychiatry 1996; 35: 997–1008.
2. Wozniak J, Beiderman J, Kiely K et al. Mania-like symptoms suggestive of childhood onset bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry 1995; 34: 867–876.
3. Faraone SV, Beiderman J, Mennin D, Wozniak J, Spencer T. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? J Am Acad Child Adolesc Psychiatry 1997; 36: 1378–1390.
4. Geller B, Luby J. Child and adolescent bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 1997; 36: 1168–1176.
5. Giedd JN. Bipolar disorder and attention-deficit/hyperactivity disorder in children and adolescents. J Clin Psychiatry 2000; 61(Suppl): 31–34.
6. Schneider SM, Atkinson DR, El-Mallakh RS. CD and ADHD in bipolar disorder. J Am Acad Child Adolesc Psychiatry 1996; 35: 1422–1423.
7. West SA, McElroy SL, Strakowski SM, Keck PE, McConville BJ. Attention-deficit hyperactivity disorder in adolescent mania. Am J Psychiatry 1995; 152: 271–273.
8. Wozniak J, Beiderman J. A pharmacological approach to the quagmire of comorbidity in juvenile mania. J Am Acad Child Adolesc Psychiatry 1996; 35: 826–827.
9. Cantwell DP. Attention deficit disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 1996; 35: 978–987.
10. Gillberg C, Melander H, von Knorring AL et al. Long-term stimulant treatment of children with ADHD symptoms. A randomized, double-blind, placebo-controlled trial. Arch Gen Psychiatry 1997; 54: 857–864.
11. Carlson GA, Rapport MD, Kelly KL, Pataki CS. The effects of methylphenidate and lithium on attention and activity level. J Am Acad Child Adolesc Psychiatry 1992; 31: 262–270.
12. Garvey MJ, Hwang S, Teubner-Rhodes D, Zander J, Rhem C. Dextroamphetamine treatment of mania. J Clin Psychiatry 1987; 48: 412–413.
13. Clower CG. Treatment of mania with dextroamphetamine. J Clin Psychiatry 1988; 49: 283.
14. Rosse RB, Johri SK, Deutsch SI. Pupilary changes associated with the development of stimulant-induced mania: a case-report. Clin Neuropharmacol 1997; 20: 270–275.
15. Koehler-Troy C, Strober M, Malenbaum R. Methyphenidate-induced mania in a prepubertal child. J Clin Psychiatry 1986; 47: 566–567.
16. Soutullo CA, DelBello MP, Ochsner JE. Severity of bipolarity in hospitalized manic adolescents with history of stimulant or antidepressant treatment. J Affect Disord 2001; (in press).
17. Strober M, DeAntonio M, Schmidt-Lacker S, Freeman R, Lampert C, Diamond J. Early childhood attention deficit hyperactivity disorder predicts poorer response to acute lithium therapy in adolescent mania. J Affect Disord 1998; 51: 145–151.
18. Anand A, Verhoeff P, Seneca N et al. Brain SPECT imaging in of amphetamine-induced dopamine release in euthymic bipolar disorder patients. Am J Psychiatry 2000; 157: 1108–1114.
19. Strakowski SM, Williams JR, Fleck DE, DelBello MP. Eight-month functional outcome following hospitalization for first episode mania. J Psychiatr Res 2000; 34: 193–200.
20. Geller B, Warner K, Williams M, Zimerman B. Prepubertal and young adolescent bipolarity versus ADHD: assessment and validity using the WASH-U-KSADS, CBCL, and TRF. J Affect Disord 1998; 51: 93–100.
21. Geller B, Zimerman B, Williams M et al. Reliability of the Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. J Am Acad Child Adolesc Psychiatry 2001; (in press).
22. Strakowski SM, Keck PE, McElroy SL et al. Twelve-month outcome after a first hospitalization for affective psychosis. Arch Gen Psychiatry 1998; 55: 49–55.
23. Duke PM, Litt IF, Gross RT. Adolescents' self-assessment of sexual maturation. Pediatrics 1990; 66: 918–920.
24. El-Mallakh RS. An open study of methylphenidate in bipolar depression. Bipolar Disord 2000; 2: 56–59.
25. Post RM, Weiss SR. Sensitization, kindling, and anticonvulsants in mania. J Clin Psychiatry 1989; 50 (Suppl): 23–30.
26. Strakowski SM, Sax KW, Setters MJ, Stanton SP, Keck PE Jr. Lack of enhanced response to repeated d-amphetamine challenge in first-episode psychosis: implications for a sensitization model of psychosis in humans. Biol Psychiatry 1997; 42: 749–755.