

## Antidepressant Exposure in Bipolar Children

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BIPOLAR disorder is increasingly diagnosed in children and adolescents. Given that antidepressants may precipitate mania, and with increased use of antidepressants in youths, it is reasonable to ask whether antidepressant administration might play a role in inducing earlier manic episodes. We reviewed all consecutive admissions with a diagnosis of bipolar disorder to a university-affiliated children's hospital, and collected information regarding previous exposure to antidepressants and stimulants. The mean age of diagnosis of bipolar disorder in our cohort was  $12 \pm SD 3.47$  years. Children who received prior antidepressant and/or stimulant treatments had an earlier bipolar diagnosis ( $10.7 \pm 3.05$  years) than children never exposed to these medications ( $12.7 \pm 4.3$  years; one-tailed  $t = -1.33$ ,  $df = 22$ ,  $p = .099$ , power = .93). Stimulants appeared to be tolerated for a longer duration than antidepressants ( $55.5 \pm 20.42$  months vs.  $6.7 \pm 8.22$  months,  $t = 6.6$ ,  $df = 12$ ,  $p = .0001$ ). Despite methodological imperfections, results indicate that children exposed to antidepressants appear to be diagnosed with bipolar disorder earlier than those never exposed to these medications. Although far from conclusive, these data are consistent with the hypothesis that antidepressant treatment is associated with a manic episode earlier than might occur spontaneously.

### INTRODUCTION

Diagnosis of bipolar disorder appears

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to be increasing in the current generation of children and adolescents. The reasons for this are unclear and probably represent a combination of factors. For example, this phenomenon may be partly a reflection of a more astute cohort of psychiatric physicians. It has been reported that the diagnosis of bipolar disorder occurs 7.5 to 8.9 years after the first mental health profession contact (Ghaemi et al. 1999; Chaemi, Boiman, and Goodwin 2000). The delay may be even longer for type II disorder—up to 11.6 years (Ghaemi et al. 2000). Consequently, earlier diagnosis of bipolar disorder may be a result of the recognition that childhood bipolar illness presents differently than the adult form (Geller and Luby 1997).

Alternatively, one may argue that, as the availability of antidepressants and mood stabilizers increased, associated diagnoses have also increased (Stoll et al. 1993). The role of antidepressants is particularly important for three reasons: 1) the first mood episode in bipolar disorder is frequently

depressive (Goodwin and Jamison 1990; Geller et al. 2001); 2) bipolar illness may share symptoms of combinations of attention deficit hyperactivity disorder (ADHD) (Wozniak et al. 1995) and conduct disorder (CD) (Carlson and Kashani 1998; Kutcher et al. 1989; Schneider, Atkinson, El-Mallakh 1996; Wozniak et al. 1995); and 3) the use of antidepressants is becoming increasingly common in treating these disorders. Several researchers have shown that, in adults, antidepressants can induce mania and can double or triple the rate of manic induction compared with spontaneous mania (Akiskal and Mallaya 1987; Altshuler et al. 1995; Amsterdam et al. 1998; Angst 1985; Ghaemi, Boiman, and Goodwin 2000; Kupfer, Carpenter, and Frank 1988; Quitkin et al. 1981; Stoll et al. 1994; Wehr and Goodwin 1979). Biederman and associates (2000) investigated the potential for manic-induction in youths. They reviewed the charts of 59 youths (mean age  $10.8 \pm SD 3.7$  years, range 3.5 - 17) with DSM-III-R bipolar disorder followed for up to 4 years; most of these children were boys (83.1%). They found that serotonin reuptake inhibiting antidepressants were associated with an increased rate of improvement in depressive symptoms (hazards ratio = 6.7,  $p = .003$ ), but were associated with a greater probability of inducing manic symptoms (hazards ratio = 3.0,  $p = .02$ ) (Biederman et al. 2000).

If antidepressants can induce mania in vulnerable children, might they be associated with earlier bipolar diagnosis? Our study examined whether children with prior treatment with antidepressants might have an earlier onset of bipolar symptoms and thus an earlier bipolar diagnosis. A retrospective chart review was undertaken to answer this question.

## METHODS

We reviewed all psychiatric inpatient and emergency psychiatric admissions for 1998 to the university-affiliated children's hospital that had a discharge diagnosis of bipolar disorder. Subjects were either currently manic/hypomanic, or had a previous history

of such episodes. The diagnosis was assigned by the clinician and was not reinvestigated retrospectively. Clinicians at this institution generally follow the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; APA 1994). The entire chart was reviewed and the following data were tabulated: age; gender; current psychiatric diagnosis; previous diagnosis; dates of these diagnoses; previous treatment with antidepressants, stimulants, or other psychotropic medications; duration of treatment with these agents; and family history of bipolar disorder. When appropriate, one-tailed *t*-tests were used to compare the groups (since the diagnosis was always made after the initiation of antidepressant/stimulant treatment). Ratios were evaluated by a test to compare proportions (El-Mallakh, Cowdry, and Pettigrew 1994). Power analysis followed (Cohen 1998).

## RESULTS

A total of 122 charts were reviewed. Forty-three (35.3%) were excluded due to a lack of full evaluation (i.e., charts for the outpatients with a diagnosis of bipolar disorder who came to the hospital for outpatient testing, and for whom only test or laboratory results were available). The remaining 79 (64.75%) charts were used as the basis of this report. Due to the retrospective nature of the design, many individual datum points were not retrievable. The cohort included 49 boys and 24 girls (8 gender information unavailable), with a mean age of 11.8 years ( $\pm SD 3.9$ , range 3-19 years). None of the charts differentiated between types I and II bipolar disorder. Sixty-one (77.2%) charts carried the diagnosis of bipolar disorder; 7 (8.9%) were bipolar disorder, not otherwise specified (NOS); and 11 (13.9%) indicated "rule-out" bipolar disorder. Medication exposure is detailed in Table 1. The average duration of antidepressant treatment was  $10.7 \pm SD 14.7$  months ( $n = 19$ ). The average duration of stimulant treatment was  $17.1 \pm 18.4$  months ( $n = 14$ ). A family history was available in 44 (55.7%) of the

TABLE 1.  
*Medication Exposure in 79 Children Studied*

Previous Treatments	Number (%)
Antidepressants alone	21 (26.6)
Antidepressants plus mood stabilizers	14 (17.7)
Any antidepressant exposure	35 (44.3)
Any stimulant exposure	29 (35.4)
Antidepressant and/or stimulant exposure	49 (62.0)
Non-antidepressant, non-stimulant medication (e.g., antipsychotics, mood stabilizers)	44 (55.7)

charts. A family history of bipolar illness was noted in only 14 subjects (17.7%). Other psychiatric family history was documented in another 30 youths (38.0%).

Age of original bipolar diagnosis was discernable in only 24 charts. In these charts, the average age of diagnosis of bipolar disorder was  $12 \pm SD 3.47$  years. The diagnosis was made when the children were  $11.28 \pm SD 3.4$  years ( $n = 7$ ) if they had received only antidepressants in the past; at 6 years if they had received only stimulants ( $n = 1$ ); at  $11.33 \pm SD 2.32$  years if they had received both antidepressants and stimulants ( $n = 6$ ); at  $10.93 \pm SD 3.05$  years if they had received either ( $n = 14$ ); and at  $12.7 \pm SD 4.23$  years if they had received neither ( $n = 10$ ).

The average duration of antidepressant treatment before the bipolar diagnosis was  $6.7 \pm 8.22$  months, and the average interval between initiation of stimulants and the bipolar diagnosis was  $55.5 \pm 20.42$  months ( $t = -6.6$ ,  $df = 12$ ,  $p = .0001$ ). This suggests that antidepressants are associated with an earlier onset of mania than stimulants. Mood stabilizers may have a protective effect. Subjects were able to be maintained on antidepressants longer if they were receiving concomitant mood stabilizer medication. Two out of 12 children taking antidepressants 2 months or less were also on mood stabilizers and 9 out of 11 subjects taking antidepressants for 1 year or more were on mood stabilizers ( $z = 3.58$ ,  $p < 0.01$ ). Children who received an antidepressant were younger ( $11.1 \pm 2.84$  years) when diagnosed with bipolar illness than those who were never exposed to stimulants ( $12.7 \pm 4.3$

years; one-tailed  $t = 1.09$ ,  $df = 21$ ,  $p = .14$ ). With the addition of stimulant exposure, the age of bipolar diagnosis dropped to  $10.7 \pm 3.05$  years (one-tailed  $t = -1.33$ ,  $df = 22$ ,  $p = .099$ ). A power analysis revealed that with the observed effect size of approximately 0.75, the current sample of 24 provided a power of 0.93. This suggests that increasing the sample size is not likely to magnify the difference between antidepressants and stimulants. The power of this study for determining if antidepressant treatment is associated with earlier onset is .57 for an effect size of less than 0.2. To have adequate power (0.8) to answer this question, a sample of over 3,800 patients is required.

Twenty-two patients (27.8%) received the bipolar diagnosis on the index admission. The remaining 57 charts had notations of a preexisting or comorbid psychiatric diagnosis. These are noted in Table 2.

## DISCUSSION

In this retrospective chart review, we found that children who had been treated with antidepressants tended to have an earlier diagnosis of bipolar disorder than those who had received stimulant treatment. These results are compatible with several interpretations. This may simply reflect an earlier age of onset of ADHD (and its associated treatment with stimulants), compared to depression (and its associated treatment with antidepressants). Alternatively, since bipolar illness tends to present as depression initially

TABLE 2.  
*Previous or Comorbid Psychiatric Diagnoses in 57 Children with Previous Psychiatric Treatment*

Diagnosis	Number of Children (%)
Bipolar Disorder	12 (21.1)
ADHD	21 (36.8)
Unipolar Depression	14 (24.6)
Obsessive–Compulsive Disorder	2 ( 3.5)
Other Anxiety Disorder	2 ( 3.5)
Autism	1 ( 1.75)
Schizophrenia	1 ( 1.75)
Adjustment Disorder	1 ( 1.75)
Personality Disorder	1 ( 1.75)

(Goodwin and Jamison 1990; Geller et al. 2001), these children may have a more severe form of bipolar illness, and consequently have their first manic episode earlier than children with comorbid ADHD. Over a third of subjects (36.8%) had previously been diagnosed with ADHD, and nearly a quarter (24.6%) had been diagnosed with depression.

Alternatively, antidepressant treatment may be more likely than stimulant treatment to precipitate an episode earlier than might occur spontaneously. The difference between antidepressants and stimulants may have important implications to treatment options in bipolar subjects. A presumed less noxious effect of stimulants is consistent with findings in adults that acute amphetamine administration may have antimanic effects (Garvey et al. 1978; Brown and Mueller 1979). Nonetheless, in a recent study with a similar design to this one, DelBello et al. (2001) found that children receiving stimulant medication had an earlier age of onset of bipolar disorder ( $10.7 \pm SD 3.9$  years,  $n = 21$ ) than children who did not receive stimulants ( $13.9 \pm 3.7$  years,  $n = 13$ ,  $p = .03$ ). This was not explained by concomitant ADHD because the age of onset of bipolar illness in children with or without ADHD was not different ( $12.0 \pm 4.2$  vs.  $11.7 \pm 4.0$  years, respectively,  $p = .6$ ) (DelBello et al. 2001). In our study there was a trend for children receiving stimulants and/or antidepressants to be diagnosed at a younger age ( $10.7 \pm$

3.05 years) than those never exposed to these medications ( $12.7 \pm 4.3$ ,  $p = .099$ ).

The observation that the duration of antidepressant treatment before the bipolar diagnosis was longer when mood stabilizers were co-administered suggests that mood stabilizers may delay antidepressant destabilization. Mood stabilizers may not have a protective effect in adult bipolar patients (El-Mallakh 1997).

One of the most striking findings of our survey is the dearth of family history of bipolar illness. In adult bipolar illness, 70% to 80% of subjects have a family history of manic-depression (Goodwin and Jamison 1990). In our sample, only 17.7% of subjects had a bipolar family history, and only 55.7% had any psychiatric history. This may represent flaws in the retrospective chart review methodology or indicate that most of these children do not suffer from a typical bipolar illness.

The design of our study places several limitations on the conclusions. Most important, we used clinical chart diagnosis rather than structured interviews. This, coupled with some of the atypical features of this population (e.g., low rates of positive family history for bipolar disorder), raises the question of the accuracy of the bipolar diagnosis. Furthermore, the retrospective nature of the data collection created many inconsistencies in the collection of key variables. Finally, the power

analysis performed suggests that the sample size is too small to avoid a type II error.

Despite these shortcomings, the study presents several important points. It appears that antidepressant treatment may alter the course of childhood bipolar illness more

strongly than stimulants. The possibility that some individuals may have experienced earlier manic episodes than would occur spontaneously raises an important question as to the safety of the use of antidepressants in children (El-Mallakh, Peters, and Waltrip 2000).

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