Published in final edited form as:

J Affect Disord. 2009 December ; 119(1-3): 16–21. doi:10.1016/j.jad.2009.02.024.

RISK FOR SWITCH FROM UNIPOLAR TO BIPOLAR DISORDER IN YOUTH WITH ADHD: A LONG TERM PROSPECTIVE CONTROLLED STUDY

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Abstract

Background—To investigate whether ADHD is a risk factor for switches from unipolar to bipolar disorder over time.

Methods—Data from two large controlled longitudinal family studies of boys and girls with and without ADHD and their siblings were used. Subjects (n=168) were followed prospectively and blindly over an average follow up period of 7 years. Comparisons were made between youth with unipolar major depression who did and did not switch to full or subthreshold BP-I disorder at the follow-up assessment. Subjects were assessed at baseline and follow-up on multiple domains of functioning. Positive family history of parental psychiatric disorders was also compared between groups.

Results—ADHD was associated with a significantly higher risk for switches from unipolar to bipolar disorder (28% vs 6%; $z=2.80$, $p=0.005$). In subjects with ADHD, switches from unipolar to

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Financial Disclosures:

Dr. Joseph Biederman is currently receiving research support from the following sources: Alza, AstraZeneca, Bristol Myers Squibb, Eli Lilly and Co., Janssen Pharmaceuticals Inc., McNeil, Merck, Organon, Otsuka, Shire, NIMH, and NICHHD. In previous years, Dr. Joseph Biederman received research support, consultation fees, or speaker's fees for/from the following additional sources: Abbott, AstraZeneca, Celltech, Cephalon, Eli Lilly and Co., Esai, Forest, Glaxo, Gliatech, Janssen, McNeil, NARSAD, NIDA, New River, Novartis, Noven, Neurosearch, Pfizer, Pharmacia, The Prechter Foundation, Shire, The Stanley Foundation, UCB Pharma, Inc. and Wyeth.

Dr. Janet Wozniak receives/d research support from, is/has been a speaker for, or is/has been on the advisory board for the following sources: Pfizer, Shire Pharmaceuticals, Eli Lilly, NIMH, and Janssen.

Dr. Stephen Faraone receives/d research support from, is/has been a speaker for, or is/has been on the advisory board for the following companies: Eli Lilly & Company, McNeil Consumer & Specialty Pharmaceuticals, Shire US Inc., Noven Pharmaceuticals, Cephalon, National Institute of Mental Health (NIMH), National Institute of Child Health and Human Development (NICHD), and National Institute of Neurological Disorders and Stroke (NINDS).

Mr. Carter Petty, Ms. Deirdre Byrne, and Ms. Patricia Wong report no conflicts of interest.

Authors Biederman, Faraone, and Wozniak designed the study and wrote the protocol. Authors Petty, Byrne, and Wong managed the literature searches and analyses. Author Petty undertook the statistical analysis, and author Biederman wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

bipolar disorder were predicted by baseline comorbid conduct disorder, school behavior problems, and a positive family history of parental mood disorder.

Limitations—Psychosis was an exclusionary criterion in the original ascertainment of the studies of ADHD probands, so we were unable to test this as a predictor of switching to BPD.

Conclusions—ADHD is a risk factor for switches from unipolar to bipolar disorder, and switches could be predicted by the presence of baseline conduct disorder, school behavior problems, and a positive family history of a mood disorder in a parent. These characteristics can aid clinicians in their treatment of youth with MDD.

Keywords

pediatric bipolar disorder; ADHD; risk factors; switch

Introduction

A high and bidirectional comorbidity between ADHD and major depressive disorder (MDD) has been well documented in the extant literature in both clinical and epidemiological samples of pediatric and adult subjects (Anderson et al., 1987; Biederman et al., 1991; Bird et al., 1988; Jensen et al., 1988; Munir et al., 1987; Woolston et al., 1989). A meta-analysis by Angold et al. (1999) provides clear documentation that ADHD significantly increases the risk for MDD several fold and that this increased risk is not due to methodological artifacts.

Pediatric MDD, in non-bipolar children, also predicts subsequent episodes of mania (Geller et al., 1994; Geller et al., 2001; Luby and Mrakotsky, 2003; Strober and Carlson, 1982a; Strober et al., 1993). In a prospective longitudinal study of 60 hospitalized, depressed adolescents, Strober et al. (1993) found that 20% switched to bipolar disorder at a 3 to 4 year follow-up. Predictors of switching to mania included rapid onset of depressive symptoms, psychomotor retardation, mood-congruent psychotic features, a family history of bipolar illness and a history of pharmacologically induced hypomania. Geller et al., (1994; 2001) followed-up 79 children with MDD and found that 32% switched to mania by an average age of 11 years and 50% by the age of 21 years. Predictors of bipolar switches included conduct symptoms and a loaded and multigenerational family history of bipolar disorder. Likewise, Luby et al (2003) found that switching to mania in a group of depressed preschoolers was associated with restlessness and a family history of bipolar disorder.

The extant literature also documents a bidirectional overlap between ADHD and bipolar disorder that has been documented in clinical and epidemiological studies of ADHD and bipolar disorder in both adults and children (Biederman et al., 2004; Biederman et al., 2000a; Biederman et al., 2000b; Biederman et al., 2003; Sachs et al., 2000). Taken together these findings raise the question as to whether ADHD represents a risk factor for switching from unipolar to bipolar disorder. Considering the severe morbidity associated with bipolar disorder in the young and the different therapeutic options required for ADHD, unipolar and bipolar disorder, a better understanding of whether ADHD represents a risk factor for switching from unipolar to bipolar disorder is of high clinical relevance. Such information can aid clinicians in the management of young depressed patients at high risk for manic episodes.

The main aims of this study were to investigate whether ADHD is a risk factor for switching from unipolar to bipolar disorder and whether such switching could be predicted based on personal and familial correlates. To this end we used data from two large prospective samples of psychiatrically and pediatrically referred boys and girls with and without ADHD and their siblings followed from childhood into late adolescence and young adult years. We hypothesized that ADHD comorbid with unipolar depression is predictive of a switch to bipolar

I disorder or subthreshold mania. We also hypothesized that patterns of comorbidity and family history would predict manic switches.

Methods

Detailed study methodology has been previously described (Biederman et al., 1996; Biederman et al., 1999; Biederman et al., 2006a; Biederman et al., 2006b). Briefly, subjects were derived from two identically designed longitudinal case-control family studies of ADHD. These studies recruited male and female probands aged 6–18 years with (n=140 boys, n=140 girls) and without (n=120 boys, n=122 girls) with ADHD ascertained from pediatric and psychiatric clinics and their siblings. Male subjects were assessed at baseline, 1-year, 4-year, and 10-year follow-ups while female subjects were assessed at baseline and a 5-year follow-up. Potential subjects were excluded if they had been adopted, or if their nuclear family was not available for study. We also excluded potential subjects if they had major sensorimotor handicaps (paralysis, deafness, blindness), psychosis, autism, inadequate command of the English language, or a Full Scale IQ less than 80. Diagnoses of parents and offspring 18 years of age and older were based on direct interviews. Diagnoses of probands and siblings less than 12 years of age were based on indirect interviews with the mothers. Probands and siblings between 12 and 17 years of age had indirect and direct interviews and a diagnosis was considered positive if either of the interviewees endorsed the disorder. Parents and adult offspring provided written informed consent to participate, and parents also provided consent for offspring under the age of 18. Children and adolescents provided written assent to participate. The human research committee at Massachusetts General Hospital approved this study.

Psychiatric assessments of subjects younger than 18 years relied on the epidemiologic version of the Schedule for Affective Disorder and Schizophrenia for Children (Kiddie SADSE) (Orvaschel, 1985, 1994). Subjects 18 years of age and older were assessed with the Structured Clinical Interview for DSM (SCID) (First et al., 1997; Spitzer et al., 1990) (supplemented with modules from the K-SADS-E to assess childhood diagnoses).

The interviewers had undergraduate degrees in psychology and were extensively trained and supervised. Based on 500 interviews the median kappa coefficient between a trained rater and an experience clinician was 0.98. Kappa coefficients for individual diagnoses included: ADHD (0.88), CD (1.0), major depression (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (0.95), and substance use disorder (1.0). We considered a diagnosis present if DSM diagnostic criteria were unequivocally met (DSM-III-R for boys' study baseline and 4-year follow-up and girls study baseline; DSM-IV for boys' study 10-year follow-up and girls' study 5-year follow-up).

A committee of board-certified child and adult psychiatrists who were blind to the subject's ADHD status, referral source, and all other data resolved diagnostic uncertainties. Diagnoses presented for review were considered positive only when the committee determined that diagnostic criteria were met to a clinically meaningful degree. We estimated the reliability of the diagnostic review process by computing kappa coefficients of agreement for clinician reviewers. For these diagnoses, the median reliability between individual clinicians and the review committee assigned diagnoses was 0.87. Kappa coefficients for individual diagnoses included: ADHD (1.0), CD (1.0), major depression (1.0), mania (0.78), separation anxiety (0.89), agoraphobia (0.80), panic (0.77), and substance use disorder (1.0). All assessment personnel were blind to proband diagnosis (ADHD or control) and ascertainment site (psychiatric or pediatric).

Mothers completed the Social Adjustment Inventory for Children and Adolescents (SAICA; John et al. 1987). Socioeconomic status (SES) was measured using the 5-point Hollingshead scale (Hollingshead, 1975).

For a full diagnosis of mania (bipolar-I disorder [(BP-I)] to be considered positive, the child had to meet full DSM criteria for a manic episode with associated impairment. Thus, a child must have met criterion A for a period (one week or longer) of extreme and persistently elevated, expansive, or irritable mood, plus criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance, plus criterion C, associated impairment. To meet for a subthreshold diagnosis of mania, a child must have met criterion A for a period of four days or longer, have at least two (three if the mood is irritable only) of the seven criterion B symptoms, and associated impairment. The approach taken by the K-SADS to evaluate bipolar disorder criteria is similar to that taken by the original SADS. First, a period of time characterized by the mood features in section A for euphoria or irritability is established. According to the K-SADS, we ask about irritability in the mania section in the following manner: Has there been a period of a week or longer when (child's name) felt super angry, grouchy, cranky or irritable all the time? So much so that (child's name) might be explosive or start fights with random people? Then each of the criteria in B is addressed. For example, to assess B1 in the mania module the interviewer would ask the mother: During this period did (child's name) feel especially self-confident? ... like he/she could do anything? ... was special? ... in what way? ... special powers? ... stronger? ... smarter? Interview questions asked to mothers and children were identical. During the interview, informants were also asked to classify the impairment associated with a given diagnosis (i.e., mild, moderate, or severe) as well as the type (i.e., counseling, pharmacotherapy, and/or hospitalization) and timing (i.e., ages of onset and offset) of any treatment for the diagnosis.

Statistical Analysis

Comparisons were made between subjects with ADHD probands and their siblings with ADHD and Control probands and their non-ADHD siblings. All subjects had unipolar major depression (MDD) at baseline **and no** BP-I disorder. A new bipolar disorder was defined as subjects meeting DSM criteria for full or subthreshold BP-I disorder within the past year of any follow-up assessment (1-year, 4-year, or 10-year follow-up for subjects in the boys' study, 5-year follow-up for subjects in the girls' study). Because the number of Controls that switched from unipolar MDD to bipolar disorder was very small (n=3), analysis of predictors of switches was restricted to ADHD subjects. Statistical tests included logistic, linear, and negative binomial regression depending on the distribution of the dependent variable (in this case, baseline predictors). To account for the non-independence of siblings, we used the Huber (Huber, 1967) correction to produce robust variances. All tests were two-tailed with alpha set at 0.05.

Results

Of 280 probands with ADHD and their 74 siblings with ADHD at baseline, 161 had a lifetime history of a major depressive episode. Of these 161 subjects, 36 were dropped because they also had a history of BP-I disorder at baseline. Of the remaining 125 subjects, 115 had follow-up data (95 probands, 20 siblings). Of 242 Control probands and their 236 siblings without ADHD at baseline, 58 had a lifetime history of a major depressive episode. Of these 58 subjects, 2 were dropped because they also had a history of BP-I disorder at baseline. Of the remaining 56 subjects, 53 had follow-up data (23 probands, 30 siblings). This yielded a total sample of 168 subjects who had a lifetime history of unipolar MDD at baseline (53 Controls, 115 ADHD). The average time from the baseline to the last assessment was 7.1 years (standard deviation=3.2 years).

Of the pool of 181 subjects at baseline with MDD and without BP-I disorder, a higher percentage of subjects from the boys' study had follow-up data (79/81, 98%) compared to the girls study (89/100, 89%, $p=0.05$). Subjects assessed at follow-up ($N=168$) were slightly older at baseline (mean=13.2 years, $SD=3.6$) than subjects lost to follow-up ($N=13$, mean=11.0 years, $SD=2.8$, $p=0.02$). There were no differences between subjects assessed at follow-up and lost to follow-up on gender ($p=0.18$), socioeconomic status (SES, $p=0.70$), or ascertainment source ($p=0.41$).

Is ADHD a risk factor for Switching from Unipolar Depression to Mania?

As shown in Figure 1, analysis of data from subjects with unipolar MDD without full or subthreshold BP-I at baseline ($N=105$ ADHD, $N=50$ Controls), showed that a significantly higher number of ADHD subjects with unipolar MDD switched to bipolar disorder at follow-up than did Controls with unipolar MDD (ADHD=27.6% [17.1% BP-I, 10.5% subthreshold BP-I] versus Controls=6.0% [4.0% BP-I, 2.0% subthreshold BP-I], $z=2.80$, $p=0.005$).

Baseline Predictors of Switching from Unipolar Depression to Mania

In ADHD subjects, subthreshold BP-I disorder at baseline significantly increased the risk for the development of a full BP-I disorder at follow up (70% vs 17%, $z=3.17$, $p=0.002$). In contrast all 3 (6%) of Controls with unipolar MDD and subthreshold bipolar disorder at baseline remitted at follow-up. Six of the subjects with ADHD and subthreshold bipolar disorder at baseline who developed full BP-I at follow-up had symptom data available at baseline. Among these, the symptom prevalences were Distractibility (100%), Flight of Ideas/Racing Thoughts (83%), Decreased Need for Sleep (67%), Irritable Mood (50%), Increased Energy and Poor Judgment (33% each), and Elated Mood, Grandiosity, and Accelerated Speech (17% each).

Comparison of baseline findings between ADHD subjects with unipolar MDD who did ($N=29$) and did not ($N=76$) switch to full or subthreshold BP-I disorder showed that the two groups did not significantly differ on age at last assessment, gender distribution, socioeconomic status, ascertainment source (pediatric versus psychiatric), or study of ascertainment (boys or girls study) (Table 1). However, subjects who switched from unipolar MDD to bipolar disorder were slightly younger at baseline and more likely to be male compared to subjects who did not switch. Therefore, baseline age and gender were statistically controlled for in all comparisons.

There were no significant differences at baseline between subjects who did and did not switch to bipolar disorder on age at onset of MDD (7.4 ± 4.4 years versus 8.0 ± 4.4 , respectively, $t=1.62$, $p=0.11$), duration of MDD (3.2 ± 3.8 versus 2.4 ± 2.9 years, respectively, $t=-1.78$, $p=0.08$), MDD associated impairment (55% versus 39% severely impaired, respectively, $z=-0.63$, $p=0.53$), use of pharmacotherapy for MDD (38% versus 30%, respectively, $z=0.26$, $p=0.79$), or need for hospitalization for MDD (3% versus 4%, respectively, $z=-0.73$, $p=0.47$). There were no meaningful differences between the groups in individual symptoms of MDD either.

In contrast, subjects who switched to bipolar disorder at follow were significantly more likely to have comorbid conduct disorder at baseline compared to subjects who did not switch (34% versus 14%, $z=2.64$, $p=0.008$) and were significantly more likely to have more "School behavior problems" compared to subjects who did not switch (83% versus 59%, $z=2.27$, $p=0.02$). In addition, subjects who switched from unipolar MDD to bipolar disorder had a significantly higher rate of parental mood disorders compared to subjects who did not switch (68% versus 35%, Figure 2). Although failing to reach our threshold for statistical significance, subjects who switched to bipolar disorder had twice the rates of parental MDD (60% versus 32%) and parental BPD (20% versus 11%).

Figure 3 shows the additive risk of the significant predictors found above. Only 5% (1/20) of subjects with no risk factors switched to bipolar disorder, while 24% (11/46) of subjects with one risk factor ($z=1.98$, $p=0.047$ versus no risk factors) and 32% (9/28) of subjects with two risk factors ($z=2.12$, $p=0.03$ versus no risk factors) switched. Subjects with all three risk factors had a significantly increased risk; 73% (8/11) of these subjects switched to bipolar disorder ($z=3.76$, $p<0.001$ versus no risk factors; $z=2.96$, $p=0.003$ versus 1 risk factor; $z=2.73$, $p=0.006$ versus 2 risk factors).

Figure 4 shows rates of BPD symptoms at follow-up in subjects who switched to full and subthreshold BP-I disorder. These rates were compared to those reported by Kowatch et al. (2005) in a meta-analysis of pediatric bipolar disorder (Figure 3). Over 80% of subjects who switched to full BP-I disorder had pressured speech, racing thoughts, distractibility, poor judgment, and increased activity, followed by over 70% with elated mood, irritable mood, and decreased sleep, and finally grandiosity (62%). Over 80% of subjects who switched to subthreshold BP-I disorder had distractibility, poor judgment, and increased activity, followed by over 40% with irritable mood, grandiosity, decreased sleep, and racing thoughts, and finally elated mood (18%) and pressured speech (36%).

Discussion

In a longitudinal analysis of children and adolescents with MDD over an average of seven years, we found that ADHD was a significant risk factor for switching from unipolar to bipolar disorder. In youth with ADHD and MDD, the risk for switching from unipolar to bipolar disorder was predicted by the presence at baseline of comorbid conduct disorder and school behavior problems, and a family history of a mood disorder in a parent.

The finding that ADHD is a risk factor for switches from unipolar to bipolar disorder is consistent with a body of literature from pediatric and adult studies of individuals with bipolar disorder and those with ADHD documenting a high and bidirectional overlap between bipolar disorder and ADHD. A weighted average of 15 studies by Angold et al. (1999) showed that 17% of youth with major depression had ADHD, while a weighted average of 7 studies by Kowatch et al. (2005) showed that 62% of youth with bipolar disorder had ADHD. The current longitudinal findings broaden these previous reports by demonstrating that the presence of ADHD marks a significant risk for children and adolescents with unipolar depression to switch to bipolar disorder over time.

Within the group of subjects with ADHD, conduct disorder at baseline conferred an additional significant risk for switching from unipolar depression to bipolar disorder at follow-up. This finding is consistent with those of Geller et al. who noted higher rates of bullying in MDD youth who switched to bipolar disorder (Geller et al., 1994). This finding is also consistent with an emergent literature linking conduct disorder to bipolar disorder (Biederman et al., 2003).

School behavior problems (as measured by the SAICA) were also significantly predictive of switching from unipolar to bipolar depression. Interestingly, this SAICA finding was specific to school behavior; problems with peers, the opposite sex, siblings, parents, and spare time did not predict switching to BPD. The items contributing to the school behavior problems are varied, including not paying attention or listening, getting into fights, being assaultive, and being overly anxious to please and concerned with rules. Future studies should seek to replicate this finding and determine specific behaviors that indicate a risk for switching from unipolar depression to bipolar disorder.

Although family histories of parental unipolar and bipolar disorder were higher in children with ADHD that switched to bipolar disorders, only the broader category of a mood disorder

was significantly more likely to be present in youth who switched to bipolar disorder (68%) versus those that did not switch (35%). This finding is consistent with a literature documenting that a family history of mood disorder is associated with pediatric bipolar disorder (Geller et al., 1994; Strober and Carlson, 1982b).

It is noteworthy that there was evidence for an additive risk of the significant predictors of bipolar switches noted above. While only 5% of subjects with no risk factors switched to bipolar disorder, 73% of subjects with all three risk factors switched to bipolar disorder. Clinicians should monitor closely subjects with ADHD and comorbid MDD with multiple risk factors for bipolar switches.

Our findings should be viewed in light of some methodological limitations. Because our sample was largely Caucasian, our results may not generalize to minority groups. Because there were very few non-ADHD subjects who switched to bipolar disorder, we were unable to test predictors of switching in youth without ADHD. Future studies should examine predictors of the risk of switching to BPD outside the context of ADHD. Although psychosis has been shown to be predictive of BPD switching (Strober et al., 1993), psychosis was an exclusionary criterion in the original ascertainment of the studies of ADHD probands, so we were unable to test this as a predictor of switching to BPD.

Despite its limitations, this is the first study to demonstrate in a longitudinal analysis that ADHD is a risk factor for switching from unipolar to bipolar disorder. In the context of ADHD, comorbid conduct disorder, school behavior problems, and a family history of parental mood disorders all increased the risk for switching from unipolar to bipolar disorder. These characteristics can aid clinicians in their treatment of youth with MDD.

Acknowledgments

This project is supported by the National Institute of Mental Health grant R01HD036317 and R03MH079954.

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Figure 1.
Rates of bipolar spectrum disorders at follow-up in subjects with MDD at baseline.

Figure 2.
Parental psychopathology in subjects who did and did not switch to BPD.

Figure 3.

Additive risk of multiple risk factors for switching to bipolar disorder (conduct disorder, school behavior problems, parental mood disorder) in ADHD subjects with MDD.

Figure 4.
BPD symptoms at follow-up in subjects who switched to BPD.

Table 1

Demographic features of subjects with MDD who did and did not switch to bipolar disorder at follow-up.

	No BPD Switch (N=76)	BPD Switch (N=29)	Test Statistic	p-value
Age at baseline (years)	12.5 ± 3.5	11.1 ± 3.2	t=-2.02	0.046
Age at last assessment (years)	19.1 ± 4.5	19.4 ± 4.2	t=0.38	0.71
Gender (male)	34 (45)	21 (72)	z=2.39	0.02
Socioeconomic status	1.9 ± 1.1	2.2 ± 1.2	z=1.37	0.17
Study of ascertainment (boys)	33 (43)	18 (62)	z=1.74	0.08
Psychiatric ascertainment source	36 (47)	19 (66)	z=1.70	0.09