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Research report

Re-examining the risk for switch from unipolar to bipolar major depressive disorder in youth with ADHD: A long term prospective longitudinal controlled study

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ABSTRACT

Background: Recent studies have identified subthreshold forms of bipolar (BP)-I disorder and deficits in emotional regulation as risk factors for bipolar disorder in youth. The primary aim of this study was to investigate whether emotional dysregulation and subthreshold forms of BP-I disorder increase the risk for BP switches in ADHD youth with non-bipolar MDD.

Methods: We used data from two large controlled longitudinal family studies of boys and girls with and without ADHD. Subjects ($N=522$) were followed prospectively and blindly over an average follow up period of 11.4 years. Comparisons were made between ADHD youth with unipolar major depression (MDD) who did ($N=24$) and did not ($N=79$) switch to BP-I disorder at follow-up.

Results: The rate of conversion to BP-I disorder at follow up was higher in MDD subjects with subthreshold BP-I disorder at baseline compared to those without (57% vs. 21%; OR=9.57, 95% CI=1.62–56.56, $p=0.013$) and in MDD subjects with deficient emotional self-regulation (OR=3.54, 95% CI=1.08–11.60, $p=0.037$).

Limitations: The sample was largely Caucasian, so these results may not generalize to minority groups. The sample of youth with SED was small, which limited the statistical power for some analyses.

Conclusions: Switches from unipolar MDD to BP-I disorder in children with ADHD and MDD were predicted by baseline subthreshold BP-I disorder symptoms and baseline deficits in emotional regulation. More work is needed to assess whether these risk factors are operant outside the context of ADHD.

1. Introduction

While it is clear that some youth with pediatric major depressive disorder (MDD) switch to bipolar (BP)-I disorder over time, the literature about predictors of such switches has been sparse. In a prospective longitudinal study of 60 hospitalized, depressed adolescents, Strober et al. (1993) found that 20% switched to bipolar disorder at a 3–4 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.

Similar findings were reported by Geller et al. (1994, 2001) who followed 79 children with MDD and found that 32% of these children switched to mania by an average age of 11 years old, and 50% switched 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 and Mrakotsky (2003) found that switching to mania in a group of depressed preschoolers was associated with restlessness and a family history of bipolar disorder. We previously reported that, among children with ADHD, switches from unipolar depression to bipolar depression were predicted by baseline comorbid conduct disorder, school behavior problems, and a positive family history of parental mood disorder (Biederman et al., 2009a).

In recent years, several lines of evidence have emerged in support of new risk factors for pediatric bipolar disorder that may also be potentially informative as predictors of bipolar switches in children with MDD. We and others documented that a unique

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profile of the Child Behavior Checklist (CBCL) consisting of marked (2 SD) elevations in the Anxiety/Depression, Aggression, and Attention (A–A–A) scales was associated with a clinical diagnosis of pediatric BP-I disorder in both epidemiological and clinical samples (Achenbach, 1991; Carlson and Kelly, 1998; Geller et al., 1998; Hazell et al., 1999; Wals et al., 2001; Mick et al., 2003) both cross-sectionally and longitudinally (Biederman et al., 2009b). Faraone et al. (2005) reported that this CBCL profile was highly efficient in identifying both lifetime and current diagnoses of BP-I disorder in ADHD youth and their siblings. Expanding on these findings, we recently reported the predictive utility of this CBCL profile for a subsequent diagnosis of BP-I disorder and associated syndrome-congruent impairments (Biederman et al., 2009a).

Likewise, a small literature has documented that subsyndromal forms of BP-I disorder are associated with a significant risk for switches to full BP-I disorder. Akiskal et al. (1985) reported on a sample of 68 youth siblings or offspring of adults with BP disorder showing that half of them developed full diagnosis of BP-I disorder during their three year follow up, particularly those with pre existing subsyndromal affective symptoms. More recently, in their longitudinal follow-up study, Birmaher et al. (2009) documented that even minor manifestations of BP-I disorder significantly increased the risk for the development of a full blown BP-I disorder over time. These authors reported that 38% of their subjects with bipolar disorder not otherwise specified converted to bipolar I or II at the 4 year follow up. Early onset, diagnosis of bipolar disorder not otherwise specified, long illness duration, low socioeconomic status, and family history of mood disorders were associated with bipolar switches. However, because these findings were derived outside the context of MDD, more work is needed to evaluate if they are also predictors of BP switches in children with MDD.

Considering the high levels of morbidity and disability associated with pediatric bipolar disorder, the identification of risk factors associated with bipolar switches is an area of very high clinical and public health significance. Identifying specific predictors of bipolar switches in the context of MDD is of particular importance because the use of antidepressants in children with MDD at risk for manic switches may precipitate manic symptoms. Such knowledge can lead to the development of more appropriate early intervention efforts aimed at both treating MDD and addressing (and thereby minimizing) the risks for BP-I. It can also guide clinicians assessing children with MDD as to the most appropriate therapeutic approaches for children at risk for bipolar switches. At the very least, the ability to reliably identify high-risk cases will support the need for careful monitoring of such children.

The primary aim of this study was to investigate whether emotional dysregulation and subthreshold forms of BP-I disorder increase the risk for BP switches in ADHD youth with non-bipolar MDD. To this end we assessed the risk of BP switches in a longitudinal sample of children with ADHD and comorbid non-bipolar MDD at baseline. Based on the literature, we hypothesized that the CBCL dysregulation profile and subthreshold symptoms of BP-I disorder *would* increase the risk for BP switches at follow up.

2. Methods

Detailed study methodology has been previously described (Biederman et al., 1996, 2006a, 2006b, 1999). Briefly, subjects were derived from two identically designed longitudinal case-control family studies of ADHD. These studies recruited male and female youth, ascertained from pediatric and psychiatric clinics, and their siblings. In the original samples, probands were children and adolescents age 6–18 with ($n=140$ boys, $n=140$ girls) and without ($n=120$ boys, $n=122$ girls) ADHD; for the purposes of this analysis, only those probands with ADHD were analyzed. Male subjects were assessed at baseline, 1-year, 4-year, and 10-year follow-ups while female subjects were assessed at baseline, 5-year, and 10-year follow-ups. 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, and blindness), psychosis, autism, inadequate command of the English language, or a Full Scale IQ less than 80.

Psychiatric diagnoses of parents and offspring 18 years of age and older were based on direct interviews. Diagnoses of subjects less than 12 years of age were based on indirect interviews with the mothers. Subjects 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 SADS-E) (Orvaschel, 1985, 1994). Subjects 18 years of age and older were assessed with the Structured Clinical Interview for DSM (SCID) (Spitzer et al., 1990; First et al., 1997) 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).

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 (1 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,