Published in final edited form as:

J Affect Disord. 2014 January ; 0: . doi:10.1016/j.jad.2013.09.036.

RE-EXAMINING THE RISK FOR SWITCH FROM UNIPOLAR TO BIPOLAR MAJOR DEPRESSIVE DISORDER IN YOUTH WITH ADHD: A LONG TERM PROSPECTIVE LONGITUDINAL CONTROLLED STUDY

© 2013 Elsevier B.V. All rights reserved.

Corresponding Author: Joseph Biederman, MD, Address: Massachusetts General Hospital, 55 Fruit Street, YAW 6A, Boston, MA 02114, Phone: 617-726-1743, Fax: 617-724-3742, jbieberman@partners.org.

CONTRIBUTORS

Dr. Biederman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Biederman substantially contributed to the conception and design, drafting, critical revision of the intellectual content, supervision, administrative/technical/material support, and funding for this manuscript. Dr. Wozniak substantially contributed to the conception and design, drafting, critical revision of the intellectual content, administrative/technical/material support, and supervision for this manuscript. Ms. Tarko substantially contributed to the data analysis and interpretation, drafting, and statistical analysis for this manuscript. Dr. Serra substantially contributed to the drafting, critical revision of the intellectual content, and administrative/technical/material support for this manuscript. Ms. Hernandez substantially contributed to the drafting, critical revision of the intellectual content, and administrative/technical/material support for this manuscript. Ms. McDermott substantially contributed to the drafting, critical revision of the intellectual content, and administrative/technical/material support for this manuscript. Ms. Woodworth substantially contributed to the drafting, critical revision of the intellectual content, and administrative/technical/material support for this manuscript. Dr. Uchida substantially contributed to the critical revision of the intellectual content of this manuscript, and administrative/technical/material support for this manuscript. Dr. Faraone substantially contributed to the conception and design, data analysis and interpretation, critical revision of the intellectual content, and statistical analysis for this manuscript. All authors have contributed to and have approved the final manuscript.

CONFLICT OF INTEREST

Dr. Joseph Biederman is currently receiving research support from the following sources: APSARD, The Department of Defense, EIMindA, Janssen, McNeil, Shire, and Vaya Pharma/Enzymotec. In 2013, Dr. Joseph Biederman received an honorarium from the MGH Psychiatry Academy for a tuition-funded CME course. He has a US Patent Application pending (Provisional Number #61/233,686) through MGH corporate licensing, on a method to prevent stimulant abuse. Dr. Biederman received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Shire and Sunovion; these royalties are paid to the Department of Psychiatry at MGH. In 2012, Dr. Joseph Biederman received an honorarium from the MGH Psychiatry Academy and The Children's Hospital of Southwest Florida/Lee Memorial Health System for tuition-funded CME courses. In 2011, Dr. Joseph Biederman gave a single unpaid talk for Juste Pharmaceutical Spain, received honoraria from the MGH Psychiatry Academy for a tuition-funded CME course, and received honoraria for presenting at international scientific conference on ADHD. He also received an honorarium from Cambridge University Press for a chapter publication. Dr. Biederman received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Eli Lilly, Shire and AstraZeneca; these royalties are paid to the Department of Psychiatry at MGH. In 2010, Dr. Joseph Biederman received a speaker's fee from a single talk given at Fundación Dr. Manuel Camelo A.C. in Monterrey Mexico. Dr. Biederman provided single consultations for Shionogi Pharma Inc. and Cipher Pharmaceuticals Inc.; the honoraria for these consultations were paid to the Department of Psychiatry at the MGH. Dr. Biederman received honoraria from the MGH Psychiatry Academy for a tuition-funded CME course.

Janet Wozniak MD is a speaker for Primedia/MGH Psychiatry Academy, and receives research support from McNeil, Shire, Janssen, and Johnson & Johnson. Her spouse, John Winkelman MD, PhD, is a consultant/advisory board for Impax Laboratories, Pfizer, UCB, Zee Inc., Sunovion, and receives research support from GlaxoSmithKline.

In the past year, Dr. Faraone received consulting income and/or research support from Akili Interactive Labs, VAYA Pharma, and SynapDx and research support from the National Institutes of Health (NIH). His institution is seeking a patent for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programs sponsored by: Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health* and Oxford University Press: *Schizophrenia: The Facts*.

Laura Tarko, Giulia Serra, Mariely Hernandez, Katie McDermott, K. Yvonne Woodworth, and Mai Uchida report no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Joseph Biederman, MD^{1,2}, Janet Wozniak, MD^{1,2}, Laura Tarko, MPH¹, Giulia Serra, MD¹, Mariely Hernandez, MA¹, Katie McDermott, BS¹, K. Yvonne Woodworth, BA¹, Mai Uchida, MD^{1,2}, and Stephen V. Faraone, PhD³

¹Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital, Boston, MA

²Department of Psychiatry, Harvard Medical School, Boston, MA

³Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY

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.

Keywords

pediatric bipolar disorder; ADHD; risk factors; switch

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 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.

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 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. 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 profile of the Child Behavior Checklist (CBCL) consisting of marked (2SD) 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.

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 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, 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; Orvaschel, 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 (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. Socioeconomic status (SES) was measured using the 5-point Hollingshead scale (Hollingshead, 1975).

The parent (usually the mother) of each participant completed the Child Behavior Checklist for ages 4 to 18 years (CBCL/4–18) (Achenbach, 1991). The CBCL queries the parent about the child's behavior in the past six months and aggregates this data into behavioral problem T-scores (Achenbach, 1991). A computer program calculates the T-scores for each scale. Raw scores are converted to gender and age standardized scores (T-scores having a mean = 50 and SD = 10). A minimum T-score of 50 is assigned to scores that fall at midpoint percentiles of 50 on the syndrome scales to permit comparison of standardized scores across scales. As described previously (Biederman et al., 2012) from the CBCL we derived the CBCL-Severe Dysregulation profile, defined as positive by a score of 210 (2 SDs above the norm) on the sum of the Attention, Aggression, and Anxious/Depressed CBCL scales (AAA profile) and the CBCL-Deficient Emotional Self Regulation (DESR) profile, defined as positive by a score of 180 (60 on average on each scale) but <210 (average T-score of 60 and <70 on AAA scales).

Statistical Analysis

We classified subjects as having a new bipolar-I disorder onset if they met DSM-IV criteria for full 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 or 10-year follow-up for subjects in the girls' study). Statistical tests included chi-squared tests, logistic regression, and cox regression. All tests were two-tailed with alpha set at 0.05.

Results

Of 280 probands with ADHD at baseline, 142 had a lifetime history of full or subthreshold major depressive disorder (MDD) at the baseline assessment. Of these 142 subjects, 26 were dropped because they also had a history of full bipolar I or II disorder at baseline. Of the remaining 116, 4 were dropped because they did not have follow-up data. This yielded a total sample of 112 subjects who had a lifetime history of unipolar MDD at baseline. From this pool, an additional 9 subjects were dropped from the analysis because they did not have information on the AAA-CBCL profile, resulting in a final sample size of 103 subjects. Of

these 103 subjects, 24 (23%) converted to full bipolar I disorder during follow-up, and 79 (77%) did not convert.

As can be seen in Table 1, there were no significant differences in age at baseline, age at last assessment, sex, or SES between subjects with MDD who did and did not switch to BP-I disorder (Table 1).

Subthreshold BP-I Disorder

The rate of conversion to BP-I disorder at follow up was significantly higher in MDD subjects with subthreshold BP-I disorder at baseline. Out of the 7 subjects with subthreshold BP-I at baseline, 4 (57%) converted to full BP-I disorder at follow-up compared with 20 out of 96 (21%) subjects with no bipolar at baseline (OR=9.57, 95%CI=1.62–56.56, $p=0.013$), even after controlling for emotional dysregulation (Table 2 and Figure 1)

Emotional Dysregulation

CBCL t-scores are standardized to age and sex in the general population; however, the numerical differences in age and sex in our sample suggested that the standard age and sex adjustments for the individual scales comprising the profile may not have been sufficient to evaluate the contribution of emotional dysregulation to BP-I switches. Thus, we ran the models adjusting for age and sex. In the adjusted analysis, the survival curves showed that while both types of emotional dysregulation (DESR and SED, as assessed by the CBCL emotional dysregulation profile) similarly increased the risk for BP-I switches (Figure 2), statistical significance could only be documented for those with DESR (OR=3.54, 95%CI=1.08–11.60, $p=0.037$) (Table 3). This is likely due to insufficient statistical power, as there were fewer than half as many subjects with SED ($n=22$) compared to the no ED ($n=42$) and DESR ($n=39$) groups.

Discussion

In this analysis from a prospectively followed longitudinal sample of ADHD youth, the presence of subthreshold BP-I symptoms and deficits in emotional regulation at baseline increased the risk for switching from unipolar MDD to BP-I disorder in later adolescence and young adulthood. While previous reports have demonstrated that the presence of ADHD marks a significant risk for switching to BP-I in children with unipolar depression (Biederman et al., 2009a), our work expands on the extant literature by identifying additional, compounding risk factors that may more precisely predict switching in this population.

The finding that subsyndromal forms of BP-I disorder in ADHD children with comorbid MDD significantly increased the risk for bipolar switches is consistent with the literature. Previous studies documented that children manifesting subsyndromal symptoms of BP-I disorder are at significant risk for conversion to full BP-I disorder over time (Akiskal et al., 1985; Birmaher et al., 2009; Goldstein and Birmaher, 2012). Taken together, past and current findings emphasize the critical importance of attending to subsyndromal manifestations of BP-I disorder in children with MDD when making therapeutic decisions, especially given the potential risk for manic activations when treated with antidepressants.

Although both moderate and severe deficits in emotional regulation, as assessed by the CBCL, increased similarly the risk for switches from unipolar MDD to bipolar disorder in ADHD children with unipolar MDD, statistical significance could only be documented for those with moderate levels of emotional dysregulation. This finding is partially discrepant to previous work (Biederman et al., 2009b) that documented that children with ADHD with a positive CBCL-severe dysregulation profile had an increased risk for a subsequent diagnosis

of BP-I disorder at the follow-up assessment. However, the previous analysis made use of a larger sample size, since it included children with and without MDD, whereas the current analysis was restricted to those with MDD. Nevertheless, these findings add support for the utility of the CBCL emotional dysregulation profiles to help identify children at high risk for compromised outcomes. (Biederman et al., 1995; Carlson and Kelly, 1998; Geller et al., 1998; Hazell et al., 1999; Wals et al., 2001; Dienes et al., 2002; Petty et al., 2007)

In previous work (Biederman et al., 2009a), we documented an additive risk of the significant risk factors for bipolar switches in ADHD youth. Comorbidity with conduct disorder, a positive family history of mood disorders, and placement in special class were independent significant risk factors for bipolar switches in ADHD youth. 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 consider subthreshold bipolar disorder and emotional dysregulation in conjunction with previously identified risk factors of switching when evaluating, treating, and monitoring youth with ADHD and comorbid MDD.

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. Our sample of youth with SED was small, which limited our statistical power for some analyses. 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.

Despite its limitations, this analysis from a longitudinal sample of ADHD children and adolescents documents that subthreshold BP-I symptoms and deficits in emotional regulation at baseline increased the risk for switching from unipolar MDD to BP-I disorder at follow up. These findings broaden those from previous reports demonstrating that comorbidity with conduct disorder and a positive family history of mood disorders are significant predictors of switches to BP-I disorder in children with ADHD.

Acknowledgments

ROLE OF FUNDING SOURCE

The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

This work was supported by NIH grants R01MH050657 and R01HD036317 to Dr Biederman. This work was also supported members of the MGH Pediatric Psychopharmacology Council.

References

- Achenbach, TM. Manual for the Child Behavior Checklist/4–18 and the 1991 Profile. University of Vermont, Department of Psychiatry; Burlington, VT: 1991.
- Akiskal HS, Downs J, Jordan P, Watson S, Daugherty D, Pruitt DB. Affective disorders in referred children and younger siblings of manic-depressives: Mode of onset and prospective course. *Arch Gen Psychiatry*. 1985; 42:996–1003. [PubMed: 4037989]
- Biederman J, Wozniak J, Kiely K, Ablon S, Faraone S, Mick E, Mundy E, Kraus I. CBCL clinical scales discriminate prepubertal children with structured-interview derived diagnosis of mania from those with ADHD. *J Am Acad Child Adolesc Psychiatry*. 1995; 34:464–471. [PubMed: 7751260]
- Biederman J, Faraone S, Milberger S, Guite J, Mick E, Chen L, Mennin D, Marrs A, Ouellette C, Moore P, Spencer T, Norman D, Wilens T, Kraus I, Perrin J. A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. *Arch Gen Psychiatry*. 1996; 53:437–446. [PubMed: 8624187]

- Biederman J, Faraone SV, Mick E, Williamson S, Wilens TE, Spencer TJ, Weber W, Jetton J, Kraus I, Pert J, Zallen B. Clinical correlates of ADHD in females: findings from a large group of girls ascertained from pediatric and psychiatric referral sources. *J Am Acad Child Adolesc Psychiatry*. 1999; 38:966–975. [PubMed: 10434488]
- Biederman J, Monuteaux M, Mick E, Spencer T, Wilens T, Klein K, Price JE, Faraone SV. Psychopathology in females with attention-deficit/hyperactivity disorder: A controlled, five-year prospective study. *Biol Psychiatry*. 2006a; 60:1098–1105. [PubMed: 16712802]
- Biederman J, Monuteaux MC, Mick E, Spencer T, Wilens TE, Silva JM, Snyder LE, Faraone SV. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. *Psychol Med*. 2006b; 36:167–179. [PubMed: 16420713]
- Biederman J, Petty CR, Byrne D, Wong P, Wozniak J, Faraone SV. Risk for switch from unipolar to bipolar disorder in youth with ADHD: A long term prospective controlled study. *J Affect Disord*. 2009a; 119:16–21. [PubMed: 19324422]
- Biederman J, Petty CR, Monuteaux MC, Evans M, Parcell T, Faraone SV, Wozniak J. The child behavior checklist-pediatric bipolar disorder profile predicts a subsequent diagnosis of bipolar disorder and associated impairments in ADHD youth growing up: a longitudinal analysis. *J Clin Psychiatry*. 2009b; 70:732–740. [PubMed: 19389330]
- Biederman J, Petty CR, Day H, Goldin RL, Spencer T, Faraone SV, Surman CB, Wozniak J. Severity of the aggression/anxiety-depression/attention child behavior checklist profile discriminates between different levels of deficits in emotional regulation in youth with attention-deficit hyperactivity disorder. *J Dev Behav Pediatr*. 2012; 33:236–243. [PubMed: 22278125]
- Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, Houck P, Ha W, Iyengar S, Kim E, Yen S, Hower H, Esposito-Smythers C, Goldstein T, Ryan N, Keller M. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. *Am J Psychiatry*. 2009; 166:795–804. [PubMed: 19448190]
- Carlson GA, Kelly KL. Manic symptoms in psychiatrically hospitalized children- what do they mean? *J Affect Disord*. 1998; 51:123–135. [PubMed: 10743845]
- Dienes KA, Chang KD, Blasey CM, Adleman NE, Steiner H. Characterization of children of bipolar parents by parent report CBCL. *J Psychiatr Res*. 2002; 36:337–345. [PubMed: 12127602]
- Faraone SV, Althoff RR, Hudziak JJ, Monuteaux MC, Biederman J. The CBCL predicts DSM bipolar disorder in children: A receiver operating characteristic curve analysis. *Bipolar Disord*. 2005; 7:518–524. [PubMed: 16403177]
- First, M.; Spitzer, R.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV Axis I Disorders. American Psychiatric Press; Washington, DC: 1997.
- Geller B, Fox L, Clark K. Rate and predictors of prepubertal bipolarity during follow-up of 6-to 12-year-old depressed children. *J Am Acad Child Adolesc Psychiatry*. 1994; 33:461–468. [PubMed: 8005898]
- Geller B, Warner K, Williams M, Zimmerman 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. [PubMed: 10743842]
- Geller B, Zimmerman B, Williams M, Bolhofner K, Craney JL. Bipolar Disorder at Prospective Follow-Up of Adults Who Had Prepubertal Major Depressive Disorder. *Am J Psychiatry*. 2001; 158:125–127. [PubMed: 11136645]
- Goldstein BI, Birmaher B. Prevalence, Clinical Presentation and Differential Diagnosis of Pediatric Bipolar Disorder. *Isr J Psychiatry Relat Sci*. 2012; 49:3–14. [PubMed: 22652925]
- Hazell P, Lewin T, Carr V. Confirmation that Child Behavior Checklist clinical scales discriminate juvenile mania from attention deficit hyperactivity disorder. *J Paediatr Child Health*. 1999; 35:199–203. [PubMed: 10365361]
- Hollingshead, AB. Four Factor Index of Social Status. Yale Press; New Haven, CT: 1975.
- Luby JL, Mrakotsky C. Depressed preschoolers with bipolar family history: a group at high risk for later switching to mania? *J Child Adolesc Psychopharmacol*. 2003; 13:187–197. [PubMed: 12880512]
- Mick E, Biederman J, Pandina G, Faraone SV. A preliminary meta-analysis of the child behavior checklist in pediatric bipolar disorder. *Biol Psychiatry*. 2003; 53:1021–1027. [PubMed: 12788247]

- Orvaschel H. Psychiatric interviews suitable for use in research with children and adolescents. *Psychopharmacol Bull.* 1985; 21:737–745. [PubMed: 4089105]
- Orvaschel, H. Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiologic Version. Nova Southeastern University, Center for Psychological Studies; Ft. Lauderdale: 1994.
- Petty CR, Rosenbaum J, Hirshfeld-Becker DR, Henin A, Hubley S, Lacasse S, Faraone SV, Biederman J. The child behavior checklist broad-band scales predict subsequent psychopathology: A five-year follow-up. *J Anxiety Disord.* 2007
- Spitzer, RL.; Williams, JB.; Gibbon, M.; First, MB. Structured Clinical Interview for DSM-III-R: Non-Patient Edition (SCID-NP, Version 1.0). American Psychiatric Press; Washington, DC: 1990.
- Strober M, Lampert C, Schmidt S, Morrell W. The course of major depressive disorder in adolescents: I. Recovery and risk of manic switching in a follow-up of psychotic and non-psychotic subtypes. *J Am Acad Child Adolesc Psychiatry.* 1993; 32:34–42. [PubMed: 8428882]
- Wals M, Hillegers MH, Reichart CG, Ormel J, Nolen WA, Verhulst FC. Prevalence of psychopathology in children of a bipolar parent. *J Am Acad Child Adolesc Psychiatry.* 2001; 40:1094–1102. [PubMed: 11556634]

Figure 1.
Cumulative Risk of Bipolar Conversion by Bipolar Status at Baseline

Figure 2.
Cumulative Risk of Bipolar Conversion

Table 1

Demographics

	No BPD switch (n=79)	BPD switch (n=24)	Test statistic	p-value
Age at baseline (years)	11.6±3.3	10.7±2.9	t=1.22	0.22
Age at last assessment (years)	21.8±5.6	24.0±4.7	t=-1.77	0.079
Gender (male)	36 (46%)	15 (63%)	$\chi^2(1)=2.11$	0.15
Socioeconomic Status	1.86±1.06	2.25±1.22	$\chi^2(1)=1.96$	0.16

Table 2

Conversion from subthreshold bipolar to full bipolar

Bipolar status at baseline	OR (95% CI)*	p-value
Subthreshold Bipolar	9.57 (1.62, 56.56)	0.013

* Compared to no bipolar at baseline, adjusted for sex, and age and ED status at baseline

Table 3

Risk for switch to bipolar by Emotional Regulation Type

Emotional Dysregulation Type	OR (95% CI)*	p-value
Any ED	2.66 (0.91, 7.83)	0.075
DESR	3.54 (1.08, 11.60)	0.037
SED	1.68 (0.43, 6.64)	0.46

* Compared to no emotional dysregulation, adjusted for sex, and age at baseline, and subthreshold bipolar status Sample size: no ED n=42, DESR n=39, SED n=22