



Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2014 April ; 53(4): 408–416. doi:10.1016/j.jaac.2013.12.026.

Disruptive Mood Dysregulation Disorder and Chronic Irritability in Youth at Familial Risk for Bipolar Disorder

Garrett M. Sparks, M.D., M.S.,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

David A. Axelson, M.D.,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Haifeng Yu, M.S.,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Wonho Ha, Ph.D.,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Javier Ballester, M.D.,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Rasim S. Diler, M.D.,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Benjamin Goldstein, M.D., Ph.D.,

Sunnybrook Health Sciences Centre, University of Toronto

Tina Goldstein, Ph.D.,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Mary Beth Hickey, B.A.,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Cecile D. Ladouceur, Ph.D.,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Kelly Monk, R.N.,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Dara Sakolsky, M.D., Ph.D., and

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Boris Birmaher, M.D.

© 2014 American Academy of Child & Adolescent Psychiatry. Published by Elsevier Inc. All rights reserved

Correspondence to: Garrett M. Sparks, M.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Bellefield Towers Room 605, Pittsburgh, PA 15213, (412) 246-5235, sparksgm@upmc.edu.

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.

Drs. Sparks, Axelson, Ha, Ballester, Diler, T. Goldstein, Ladouceur, and Sakolsky, and Mr. Yu, Ms. Hickey, and Ms. Monk report no biomedical financial interests or potential conflicts of interest.

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Abstract

Objective—Disruptive mood dysregulation disorder (DMDD) is a new diagnosis in the DSM-5. Youth with a family history of BD are at increased risk for BD and non-bipolar psychopathology. No studies to date have examined rates of DMDD among offspring of parents with BD. This study examines the risk for DMDD in offspring of parents with BD compared to community controls and considers rates of chronic irritability (independent of a DMDD diagnosis) across diagnoses in youth with parents with BD.

Method—Modified DMDD criteria were applied post hoc to 375 offspring of parents with BD and 241 offspring of community control parents aged 6–17. We calculated odds ratios using generalized linear mixed models. Additionally, we explored associations with a severe chronic irritability phenotype and various diagnoses in the high risk cohort.

Results—Offspring of parents with BD were more likely to meet criteria for DMDD than the offspring of community control parents (OR=8.3, 6.7% vs 0.8%), even when controlling for demographic variables and comorbid parental diagnoses (OR 5.4). They also had higher rates of chronic irritability compared to community controls (12.5% vs. 2.5%, $\chi^2=18.8$, $p<0.005$). Within the offspring of parents with BD, the chronic irritability phenotype was frequently present in offspring with diagnoses of BD, depression, ADHD, and DBD.

Conclusions—Like other non-BD diagnoses, family history of BD increases the risk for DMDD. Severe chronic irritability and temper tantrums are the core features of DMDD and are associated with mood and behavioral disorders in youth at risk for BD.

Keywords

bipolar disorder; high risk; offspring; familial; disruptive mood dysregulation disorder

Introduction

The relative increase in the diagnosis of pediatric bipolar disorder (BD) over the past two decades^{1–4} has prompted substantial debate about how a disorder once thought to occur almost exclusively in adults presents in children and adolescents. A recent meta-analysis estimated that the rate of BD in youth across U.S. and non-U.S. samples is 1.8%, with the highest estimates coming from studies that used the broadest definitions of BD⁵. Some researchers advocated that youth with severe chronic irritability and other symptoms of mania shared with attention deficit hyperactivity disorder (ADHD) are best conceptualized as suffering from a bipolar spectrum disorder^{6–9}, while the others have argued against assigning a bipolar spectrum diagnosis to these children^{10–14}.

Irritability is a ubiquitous symptom of many childhood psychiatric disorders and is a DSM-V criterion for BD, major depressive disorder (MDD), generalized anxiety disorder (GAD), and oppositional defiant disorder (ODD). Recent studies suggest that youth with severe chronic non-episodic irritability may have substantially lower rates of progression to BD-I or -II compared to youth who meet operationalized criteria for episodic Bipolar Disorder

Not Otherwise Specified (BD-NOS)¹⁵⁻¹⁸. Most studies have shown that severe chronic irritability in youth predicts a later diagnosis of unipolar depression and anxiety disorders over twenty years of follow-up^{19,20}, while there is some limited data to suggest possible association with later development of BD^{21,22}. Another study specifically identifies anxiety rather than irritability as a later predictor of BD²³. Severe chronic irritability appears to be a non-specific aspect of the development of many later diagnoses^{22,24}.

In order to better characterize youth with chronic irritability who might otherwise be assigned a diagnosis of BD²⁵, investigators at the NIMH Intramural Mood and Anxiety Program established criteria for a syndrome of chronic irritability with explosive outbursts and hyperarousal symptoms designated as severe mood dysregulation (SMD)²⁶. Youth with SMD demonstrate chronic irritability rather than discrete episodes of mania but display high levels of impairment similar to youth with BD²⁵. A case-control study found that youth with SMD have much lower rates of familial BD than youth with BD²⁷. Secondary analyses of longitudinal epidemiological studies have demonstrated that youth with an operationalized diagnosis of SMD, similarly to youth with ODD, are significantly more likely to be diagnosed with a depressive disorder on an average of 8 years of follow-up²⁸.

A new diagnosis, Disruptive Mood Dysregulation Disorder (DMDD) was recently included in the DSM-5²⁹ based largely on research on SMD. Criteria for DMDD are similar to SMD, with the exception that the SMD hyperarousal symptoms were removed from the criteria for DMDD, the upper boundary of the age of onset is set earlier at age 10, and an ODD diagnosis is excluded with a DMDD diagnosis. The hallmark symptoms of DMDD are recurrent severe temper outbursts in context of a chronically irritable mood. DMDD shares many characteristics of ODD including irritable mood and temper outbursts. The irritable dimension of ODD, not the oppositional component, predicts later mood and anxiety disorders^{30,31}.

Published research on DMDD as a diagnostic category is limited³². Post hoc analysis of existing studies, such as a recent analysis of multiple epidemiologic studies³³, may be of some utility in further informing our understanding of DMDD.

The single best predictive factor associated with risk of developing BD is high family loading for the disorder³⁴. The Pittsburgh Bipolar Offspring Study (BIOS) is a single site cohort study following offspring of parents with BD as well as offspring of parents from a demographically matched community sample³⁵. The initial publication from the study reported an increased rate of mood disorders and anxiety disorders for offspring of parents with BD compared to offspring of control parents, including odds ratios (ORs) of 13.4 for a bipolar spectrum disorder, 2.1 for a depressive disorder, and 2.3 for anxiety disorders. After controlling for demographic factors, offspring of parents with BD did not have significantly higher rates of ADHD than controls. Offspring of parents with BD with high socioeconomic status (SES) had higher rates of ODD and conduct disorder (CD) compared to control offspring, though this was not true at lower SES.

The primary objective of this current study was to evaluate whether the offspring of parents with BD were more likely to meet modified criteria for DMDD than offspring of parents

without BD, and whether this would be better accounted for by higher rates of other diagnoses in parents with BD³⁵. As detailed below, the DMDD criteria were modified because at the time of the original study existing assessment tools did not include specifically all aspects of the DSM-5 criteria, though much of this information could be gleaned from the assessment instruments and narrative summaries previously collected. Similar methods have been used in recent publications^{33,36}. We secondarily explored rates of a chronic irritability phenotype, defined using only DMDD symptom criteria A–D, capturing youth with frequent temper outbursts in context of severe chronic irritability independent of their diagnosis.

We hypothesized that offspring of parents with BD would be at higher risk for DMDD than offspring of community control parents, and this difference would not be accounted for entirely by comorbid non-BD parental diagnoses. Additionally, we compared the demographic and clinical characteristics of offspring of parents with BD who did or did not meet DMDD criteria. Additionally, we hypothesized that the chronic irritability phenotype will be common in youth at familial risk for BD with mood and anxiety disorders, ODD, CD, and ADHD.

Method

Subjects

The methods for the Pittsburgh Bipolar Offspring Study have been described in detail elsewhere^{35,37–39}. A summary is provided below.

Parents (Probands)—Parents with BD (n=233) were recruited through advertisement (53%), adult BD studies (31%), and outpatient clinics (16%). There were no differences in BD subtype, age of BD onset, or rates of non-BD disorders on the basis of recruitment source. Parents were required to fulfill Diagnostic and Statistical Manual, Version-IV (DSM-IV) criteria for BD-I or -II. Exclusion criteria included current or lifetime diagnoses of schizophrenia, mental retardation, mood disorders secondary to substance abuse, medical conditions, or medications, and living more than 200 miles away from Pittsburgh.

Parents (Controls)—Control parents (n=143) consisted of healthy parents and parents with non-BD psychiatric disorders from the community group matched by age, sex, and neighborhood using the zip codes and the area code and first 3 digits of telephone numbers. The exclusion criteria for the control parents were the same as those for parents with BD, with the additional requirements that neither biological parent could have BD, and they could not have a first-degree relative with BD. Control parents were recruited by the University Center for Social and Urban Research, University of Pittsburgh in an approximate ratio of 1 control parent for every 2 parents with BD.

Offspring

With the exception of children who were unable to participate (e.g., mental retardation), all offspring ages 6 through 17 years from each family were included in the study (n=375

offspring of parents with BD, 241 offspring of control parents), with a single exception described below.

Procedures

After receiving Institutional Review Board approval and obtaining written informed consent from parents and assent from children, parents were assessed for psychiatric disorders and other variables. DSM-IV psychiatric disorders for proband parents were ascertained through the Structured Clinical Interview-DSM-IV (SCID)⁴⁰ plus the ADHD, Disruptive Behavior Disorders (DBD), and Separation Anxiety Disorder (SAD) sections from the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL)⁴¹.

Parents were interviewed about their children, and the offspring were directly interviewed for the presence of lifetime non-mood psychiatric disorders using the K-SADS-PL. Mood disorders were evaluated using the K-SADS Mania Rating Scale and the depression section of the KSADS-Present Episode version, modified to assess lifetime mood disorders. As per the KSADS instructions, mood symptoms that were also in common with other psychiatric disorders (e.g., hyperactivity) were not rated as present in the mood section unless they intensified with the onset of abnormal mood. Comorbid diagnoses were not assigned if they occurred exclusively during a mood episode.

All diagnoses were made using DSM-IV criteria, with the exception of DMDD, which is described in detail below. We used the operationalized criteria for BD-NOS from the COBY study^{15,42,43}. In most cases, youth with BD-NOS in COBY did not meet criteria for BD-I or -II because of insufficient duration of symptoms rather than insufficient number of symptoms. With the exception of BD-NOS in children, other NOS and adjustment disorders for children or adults were not included in these analyses.

Bachelor's- or Master's-level interviewers completed all assessments after intensive training for all instruments and after 80% agreement with a certified rater.

Approximately 90% of assessments were carried out in the subjects' homes. To ensure blindness to parental diagnoses, the interviewers who met with the parent to assess parental psychopathology were different from the interviewers who assessed their children's psychopathology. When necessary, subjects' medical and psychiatric records were obtained and reviewed by their respective interviewers. All data were presented to a child psychiatrist for diagnostic confirmation. The child psychiatrists were also blind to the psychiatric status of the parents.

SES was ascertained using the Hollingshead scale⁴⁴. Offspring psychosocial functioning at intake was assessed using the Children's Global Assessment Scale (C-GAS)⁴⁵.

DMDD Diagnosis

DMDD was not proposed at the time of the design of the study and employed instruments did not ascertain specifically all of the criteria for the disorder, though the cardinal symptoms of most interest are assessed in detail. When the instruments did not provide

information, we reviewed the narrative summaries of the clinical presentations. The following criteria were used to evaluate the presence of DMDD in our sample. The score on the current temper outburst item on the K-SADS ODD screen reflected frequent, severe temper outbursts occurring 2–5 times per week for the past 6 months (Criteria A–C). The ratings for both the “easily annoyed” and “angry” items on the KSADS ODD supplement were “daily or almost daily,” (Criterion D). Duration criteria of 6 months were assessed in the original ODD supplement, but narrative summaries were reviewed to confirm persistence of symptoms for 12 months (Criterion E). Impairment was present in at least 2 out of 3 contexts (home, school, and/or with peers) (Criterion F). Children were all at least 6 years of age (Criterion G). Age of onset before age 10 (Criterion H) and symptoms occurring only in the context of other disorders (Criterion J) were assessed by reviewing the narrative summaries. We wish to emphasize for clarity the important criterion that any subject with a diagnosis of any BD spectrum disorder was disqualified from a DMDD diagnosis (Criterion I). Similar approaches have been applied to other large studies to evaluate the prevalence of SMD²⁸ and DMDD^{33,36}. One subject was excluded from the analysis entirely because the narrative did not allow us to determine whether he should be assigned a DMDD diagnosis due to unclear age of onset and duration.

Chronic Irritability Phenotype

In the secondary analysis, we specifically focused on the DMDD symptom criteria A–D, which includes the items for severe chronic irritability and inappropriate temper outbursts. To avoid confusion with the DMDD diagnosis, the label “chronic irritability phenotype” was applied to children who met criteria A–D (regardless of whether they met full DMDD criteria). The DMDD criteria A–D are an elegant proxy for the clinical presentation of the explosive, irritable child so frequently seen in the clinical practice of child and adolescent psychiatry. As we focused upon the presence of these particular symptoms without regard to age limits, other diagnoses, or any other exclusionary criteria, diagnoses which would exclude a diagnosis of DMDD, such as BD, are included in this analysis. By not excluding these diagnostic categories, the chronic irritability phenotype in youth with a parent with BD could be considered across diagnoses.

Statistical Analyses

Standard parametric and nonparametric statistical tests were used as appropriate to examine the group rates of DMDD and associated factors.

Odds Ratios (ORs) to estimate the risk of DMDD based on status as offspring of bipolar parents or community control parents were calculated using generalized linear mixed models with family of origin used as a random effect variable. The model was initially constructed as a univariate model. Subsequently, demographic variables (age, gender, race, SES, and offspring living with both biological parents) and proband parent non-BD lifetime diagnoses (ADHD, depressive disorder, anxiety disorder, ODD/CD, and substance use disorder) were entered as potential covariates. Models were constructed with backward model selection procedures, removing demographic variables and parental diagnoses with $p > 0.10$ iteratively in order of magnitude until all variables remaining in the model were significant. Similar procedures were used to examine the association of DMDD and offspring diagnoses in the

offspring of parents with BD. Given diagnostic overlap between DMDD and ODD, offspring ODD was not included in the final multivariate model.

Results

DMDD in offspring of parents with BD vs. offspring of community controls

Offspring of parents with BD were significantly more likely to meet criteria for DMDD than offspring of community control parents, $\chi^2=11.9$, $p=0.001$. Twenty-five (6.7%) offspring of parents with BD met criteria for DMDD (mean age 10.5, range 6.5–17.5, 13/25 female), while only 2 (0.8%) of the offspring of community control parents met criteria for DMDD. There were no statistically significant demographic differences between the two groups.

In a univariate model, having a parent with BD was associated with an eight-fold increase in the risk of DMDD over offspring of control parents (OR=8.3, 95% CI 1.9–36.0) (Table 1). In the multivariate model, after backward model selection elimination of demographic and parent diagnosis variables with $p>0.10$, having a parent with BD (OR 5.4, 95% CI 1.2–24.5) and having a parent with ADHD (OR 3.7, 95% CI 1.6–8.7) conferred increased risk for DMDD.

Factors associated with DMDD in the offspring of parents with BD

Demographic variables were not significantly associated with DMDD among offspring of parents with BD (Table 2). Offspring who met DMDD criteria were more likely to have a parent with comorbid BD and ADHD in comparison to the offspring who did not meet DMDD criteria. Offspring with DMDD also had higher rates of ADHD, ODD, and CD, as well as worse overall functioning (all $p<0.05$) than their non-DMDD peers. Depressive disorders were more common in offspring with DMDD, though there were only 3 (12.0%) offspring with DMDD with MDD, compared to 31 (8.9%) without DMDD. There were no significant group differences in rates of SUD or anxiety disorders. The C-GAS at time of intake was significantly lower in youth who met criteria for DMDD.

Nearly all of the offspring of a bipolar parent who met DMDD criteria also met for either CD (8/25) or ODD (16/25). If CD were not applied as an exclusion criteria for ODD, then 23/25 met criteria for ODD, with only one subject meeting criteria for CD but not ODD.

In addition, DMDD substantially overlapped with ADHD comorbid with either ODD or CD, as 8/25 of the offspring with DMDD had comorbid ADHD and ODD, and an additional 7/25 had comorbid ADHD and CD.

A multivariate model was constructed to evaluate the association between DMDD and the diagnoses of depressive disorders, ADHD, anxiety disorders, and CD in the offspring of parents with BD (Table 3). Offspring ADHD tripled the risk for DMDD (OR 3.1, 95% CI 1.2–8.2), and offspring CD increased risk for DMDD by nearly twenty-fold (OR 18.8, 95% CI 4.9–71.3). Also retained in the model after backward model selection procedures were offspring depressive disorders (OR 2.4, $p=0.082$).

Chronic irritability phenotype in offspring of parents with BD vs. offspring of community controls

Offspring of parents with BD were much more likely to display the chronic irritability phenotype, $\chi^2=18.8$, $p<0.005$. Forty-seven (12.5%) out of 375 offspring of parents with BD displayed the chronic irritability phenotype, while only 6/241 (2.5%) displayed the chronic irritability phenotype in the offspring of control parents.

Chronic irritability phenotype by diagnosis in the offspring of parents with BD

Several diagnoses are associated with an increased rate of the chronic irritability phenotype in the offspring of parents with BD (Table 4). The chronic irritability phenotype was commonly present in any BD (10/33, 30.3%), particularly in BD-I or -II (5/12, 41.7%), any depressive disorder (13/41, 31.7%) ADHD (23/93, 24.7%), ODD (27/58, 46.6%), and CD (12/14, 85.7%). All of the offspring who met criteria for both ADHD and CD displayed the chronic irritability phenotype.

Discussion

This study examined the rates of the DMDD diagnosis as well as a severe chronic irritability phenotype in the offspring of parents with BD and community controls, as well as factors associated with DMDD in youth at familial risk for BD. We found that the offspring of parents with BD were more than eight times more likely to meet DMDD criteria than the offspring of community control parents, and 5.4 times more likely after controlling for demographic variables and other parental diagnoses, most significantly parental ADHD, which itself increased risk for DMDD by a factor of nearly 4. Similarly, the offspring of parents with BD had much higher rates of severe chronic irritability as compared to community controls (12.5% vs. 2.5%). As previously reported in this sample³⁵, the offspring of a parent with BD are at increased risk for BD and non-BD psychopathology, including depressive disorders, anxiety disorders, DBD, and ADHD. However, when controlling for demographic variables and parental diagnoses, the only non-BD disorder that remained at higher risk was anxiety disorders (OR=2.3), as depressive disorders (OR=2.1), DBD (OR=2.1), and ADHD (OR=1.4) were no longer statistically significantly higher in the offspring of parents with BD. This study indicates that at intake, DMDD has a numerically higher magnitude of association with having a parent with BD as compared to other non-BD diagnoses.

Among the offspring of a bipolar parent, depressive disorders, ADHD, CD were associated with increased risk for meeting criteria for DMDD, whereas anxiety disorders, contrary to our hypothesis, were not. All but one of the youth with DMDD (24/25) also met criteria for either ODD (if permitted) or CD. Offspring with DMDD were substantially more impaired than their non-DMDD peers.

The offspring of parents with BD with chronic irritability and frequent temper outbursts (chronic irritability phenotype) had significantly higher rates of BD-I or -II, ADHD, ODD, and CD. Among the 47 offspring of parents with BD who displayed the chronic irritability phenotype, 39 (83.0%) met criteria for either ODD or CD. In the offspring of parents with

BD, the chronic irritability phenotype was observed in nearly one-quarter of the offspring with ADHD, one-third of the offspring with BD-I or -II, half of the youth with ODD, and nearly all of the offspring with CD.

The above findings must be interpreted in the context of various limitations inherent to this study. First, DMDD criteria were applied post hoc using the ODD supplement of the KSADS-PL which was not specifically designed to assign a diagnosis of DMDD. However, the criteria used were very close to the DSM-5 criteria. Moreover, our approach was similar to that used to study SMD in the Great Smoky Mountains Study²⁸, as well as studies of DMDD in other post hoc studies employing similar methodologies^{33,36}. Of the 53 youth who displayed the chronic irritability phenotype across the subject groups, 14 did not meet age of onset criteria, 4 did not meet duration criteria, 10 were not impaired in more than one setting, and 10 met criteria for a BD spectrum disorder. Symptoms only occurred in the context of a mood disorder in 2 subjects. Although our approach rigorously assessed DMDD criteria using available information, it is not entirely clear if the diagnosis might have been assigned differently using methods designed a priori to identify DMDD. The narrative summaries clearly revealed the symptom criteria for which they were used in all but one subject, who was excluded from the analysis. As the ODD supplement is employed whenever frequent severe temper outbursts are present, false negatives are unlikely.

Second, very few offspring of community control parents met criteria for DMDD. This is comparable to rates of operationalized DMDD (0.8–3.3%)³³ in Copeland's study. Because of our sample size, we were unable to draw conclusions about offspring of control parents who met criteria for DMDD. The findings of this study may have little bearing on youth who do not have a parent with BD.

Third, the young mean age of offspring examined in the study suggests that the majority of the sample has yet to traverse the period of greatest risk for BD or other mood and anxiety disorders, and possibly DMDD itself. These analyses are cross-sectional and used lifetime diagnoses for child and parental psychopathology, while the DMDD diagnosis was assigned if symptoms were present at the time of the initial assessment into the BIOS study. Given the cross-sectional design, we are unable to determine whether DMDD may predict increased or decreased risk for the later onset of other disorders.

Despite these limitations, this study adds to the limited literature on DMDD, examining the rates of a DMDD in a large sample of youth at high risk for a wide variety of psychiatric diagnoses. This high risk sample is particularly relevant given that one rationale for the inclusion of DMDD in the DSM-5 is that criteria for BD are being misapplied to youth with chronic irritability who do not have distinct episodes of manic symptoms³². In this study, about one-third of the offspring with BD displayed chronic irritability and frequent temper outbursts, though the presence of hypomania or mania excludes the DMDD diagnosis. These findings highlight the tremendous importance of screening for and applying exclusion criteria before diagnosing DMDD, particularly in offspring of parents with BD. While DMDD does not lie on the bipolar spectrum any more than other non-bipolar diagnostic categories, severe chronic irritability is not uncommon in BD, and a failure to apply

exclusion criteria carefully, including a thorough screen for hypomania/mania, could lead to misdiagnosis.

All but one of the offspring of parents with BD who met DMDD criteria would meet criteria for ODD or CD as well (though a DMDD diagnosis excludes the ODD diagnosis). In addition, 60% of the DMDD offspring met criteria for both ADHD and either ODD or CD. The markedly increased risk for DMDD in offspring with CD would not be predicted based on overlapping criteria alone.

The results of this high risk offspring study suggest that severe chronic irritability with frequent temper outbursts are also commonly associated with other disorders, including ADHD, ODD/CD, and mood disorders, including BD. Similarly, using a dimensional approach examining a sample from BIOS aged 6–18, Diler et al⁴⁶ found that, compared with offspring of control parents, the offspring of parents with BD had elevated levels of mood dysregulation (CBCL-DP subscale) as well as mood lability (impulsivity, irritability, temper outbursts, etc.). Previous studies report that youth who met criteria for SMD had very low rates of manic or hypomanic episodes on follow-up compared to youth diagnosed with BD¹⁶ and had low rates of familial BD²⁷. In our study, youth at risk for BD met criteria for DMDD at higher rates compared to community controls. However, this cross-sectional study cannot determine whether offspring of parents with BD who meet criteria for DMDD are at higher or lower risk to develop BD in the future. Several hypotheses could be generated. For one, the absence of distinct hypomania or mania episodes at onset of severe chronic irritability could actually signal a low risk of later conversion to BD (as seen in the SMD study). Alternatively, as these high risk youth had not yet reached the age of highest vulnerability for BD, youth who may later develop BD could possibly present with severe chronically irritability prior to the onset of hypomania or mania episodes. As family history is such a potent risk factor for development of BD, further investigation will reveal whether having a family history of BD could predict a distinct developmental trajectory for youth with DMDD.

Despite our finding that the risk of DMDD in youth with parents who have BD is increased compared to those who do not share this genetic predisposition, this does not mean that DMDD is on the bipolar spectrum. Parental bipolar disorder increases the risk for multiple categories of childhood psychopathology, and DMDD is no more on the bipolar spectrum than are anxiety disorders, MDD, or ADHD. However, each of these disorders may share more basic deficits of neurocircuitry and affective regulation skills. Chronic irritability represents a common vulnerability among children who suffer from a variety of disorders. As investigations increasingly move away from categorical diagnoses towards basic domains of functioning, we will learn the degree to which emotional dysregulation is similar or dissimilar across the diagnostic categories we currently use to conceptualize our patients.

A diagnosis of DMDD may substantially impact future treatment recommendations, though at this time there is limited data available to directly inform treatment of DMDD. A small study of lithium (n=14) vs. placebo (n=11) was ineffective for treatment of SMD⁴⁷, while a small (n=21) open-label trial showed that risperidone reduced irritability in SMD⁴⁸. The

diagnostic stability of DMDD is not known in youth at risk for BD, and optimal treatment approaches may differ in this population.

In a longitudinal study comparing youth with SMD and BD¹⁶, only one participant with SMD experienced a manic or hypomanic episode after two year follow-up. The authors note that the participant with SMD who experienced the manic or hypomanic episode had first and second degree relatives with BD. Longitudinal studies could elucidate whether severe chronic irritability in the offspring of a parent with BD may be associated with a differential risk for later development of BD.

Acknowledgments

This research was supported by a grant from the National Institute of Mental Health (NIMH), R01MH60952 (BB).

Wonho Ha, Ph.D., and Haifeng Yu, M.S., served as statistical experts for this study.

Thanks to the families for their participation and Melissa Cade, BS, University of Pittsburgh, School of Medicine, for her administrative support.

Disclosures: Dr. B. Goldstein has received grant or research support from the Canadian Institute of Health Research, the Depressive and Bipolar Disorder Alternative Treatment Foundation, the Heart and Stroke Foundation of Ontario, NIMH, and the Ontario Mental Health Foundation; has served as a consultant to Bristol-Myers Squibb; and has received honoraria from Purdue Pharma. Dr. Birmaher receives research support from the National Institutes of Mental Health. He receives royalties from Random House, Inc. (New Hope for Children and Teens with Bipolar Disorder), Lippincott Williams and Wilkins (Treating Child and Adolescent Depression), and UpToDate.

References

1. Harpaz-Rotem I, Rosenheck R. Changes in outpatient psychiatric diagnosis in privately insured children and adolescents from 1995 to 2000. *Child Psychiatry Hum Dev.* 2004; 34(4):329–340. [PubMed: 15039605]
2. Harpaz-Rotem I, Leslie D, Martin A, Rosenheck R. Changes in child and adolescent inpatient psychiatric admission diagnoses between 1995 and 2000. *Soc Psychiatry Psychiatr Epidemiol.* 2005; 40(Aug)(8):642–647. [PubMed: 16133747]
3. Blader J, Carlson G. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients 1996–2004. *Biol Psychiatry.* 2007 Jul 15; 62(2):107–114. [PubMed: 17306773]
4. Moreno C, Laje G, Blanco C, Jiang H, Schmidt A, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry.* 2007; 64(9):1032–1039. [PubMed: 17768268]
5. Van Meter A, Moreira A, Youngstrom E. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. *J Clin Psychiatry.* 2011 Sep; 72(9):1250–1256. 2011. [PubMed: 21672501]
6. Biederman J, Klein R, Pine D, Klein D. Resolved: mania is mistaken for ADHD in prepubertal children. *J Am Acad Child Adolesc Psychiatry.* 1998; 1998(37):10. [PubMed: 9444889]
7. Mick E, Spencer T, Wozniak J, Biederman J. Heterogeneity of irritability in attention-deficit/hyperactivity disorder subjects with and without mood disorders. *Biol Psychiatry.* 2005 Oct 1; 58(7):576–582. [PubMed: 16084859]
8. Wozniak J, Biederman J, Kwon A, et al. How cardinal are cardinal symptoms in pediatric bipolar disorder? An examination of clinical correlates. *Biol Psychiatry.* 2005 Oct 1; 58(7):583–588. [PubMed: 16197929]
9. Mick E, Biederman J, Faraone SV, Murray K, Wozniak J. Defining a developmental subtype of bipolar disorder in a sample of nonreferred adults by age at onset. *J Child Adolesc Psychopharmacol.* 2003 Winter;13(4):453–462. [PubMed: 14977458]
10. Carlson GA. Mania and ADHD: comorbidity or confusion. *J Affect Disord.* 1998 Nov; 51(2):177–187. [PubMed: 10743850]

11. 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 Nov; 51(2):93–100. [PubMed: 10743842]
12. Geller B, Williams M, Zimmerman B, Frazier J, Beringer L, Warner KL. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. *J Affect Disord.* 1998 Nov; 51(2):81–91. [PubMed: 10743841]
13. Diler RS, Birmaher B, Axelson D, et al. The Child Behavior Checklist (CBCL) and the CBCL-bipolar phenotype are not useful in diagnosing pediatric bipolar disorder. *J Child Adolesc Psychopharmacol.* 2009 Feb; 19(1):23–30. [PubMed: 19232020]
14. Doerfler LA, Connor DF, Toscano PF Jr. Aggression, ADHD symptoms, and dysphoria in children and adolescents diagnosed with bipolar disorder and ADHD. *J Affect Disord.* 2011 Jun; 131(1–3): 312–319. [PubMed: 21168917]
15. Axelson D, Birmaher B, Strober M, et al. Course of subthreshold bipolar disorder in youth: diagnostic progression from bipolar disorder not otherwise specified. *J Am Acad Child Adolesc Psychiatry.* 2011 Oct; 50(10):1001–1016. [PubMed: 21961775]
16. Stringaris A, Baroni A, Haimm C, et al. Pediatric bipolar disorder versus severe mood dysregulation: risk for manic episodes on follow-up. *J Am Acad Child Adolesc Psychiatry.* 2010 Apr; 49(4):397–405. [PubMed: 20410732]
17. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry.* 2006; 63(2):175–183. [PubMed: 16461861]
18. Halperin JM, Rucklidge JJ, Powers RL, Miller CJ, Newcorn JH. Childhood CBCL bipolar profile and adolescent/young adult personality disorders: a 9-year follow-up. *J Affect Disord.* 2011 Apr; 130(1–2):155–161. [PubMed: 21056910]
19. Stringaris A, Cohen P, Pine D, Leibenluft E. Adult outcomes of youth irritability: a 20-year prospective community-based study. *Am J Psychiatry.* 2009; 166(9):1048–1054. [PubMed: 19570932]
20. Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley TC. Adolescent irritability: phenotypic associations and genetic links with depressed mood. *Am J Psychiatry.* 2012 Jan; 169(1):47–54. [PubMed: 22193524]
21. Fergus EL, Miller RB, Luckenbaugh DA, et al. Is there progression from irritability/dyscontrol to major depressive and manic symptoms? A retrospective community survey of parents of bipolar children. *J Affect Disord.* 2003 Oct; 77(1):71–78. [PubMed: 14550937]
22. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry.* 2003 Jul; 60(7):709–717. [PubMed: 12860775]
23. Johnson JG, Cohen P, Brook JS. Associations between bipolar disorder and other psychiatric disorders during adolescence and early adulthood: a community-based longitudinal investigation. *Am J Psychiatry.* 2000 Oct; 157(10):1679–1681. [PubMed: 11007724]
24. Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch Gen Psychiatry.* 2009 Jul; 66(7):764–772. [PubMed: 19581568]
25. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am J Psychiatry.* 2011 Feb; 168(2):129–142. [PubMed: 21123313]
26. Leibenluft E, Charney D, Towbin K, Bhangoo R, Pine D. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry.* 2003 Mar; 160(3):430–437. [PubMed: 12611821]
27. Brotman MA, Kassem L, Reising MM, et al. Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation. *Am J Psychiatry.* 2007 Aug; 164(8):1238–1241. [PubMed: 17671287]
28. Brotman MA, Schmajuk M, Rich BA, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biol Psychiatry.* 2006 Nov 1; 60(9):991–997. [PubMed: 17056393]
29. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition. Washington, DC: American Psychiatric Publishing; 2013.

30. Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: irritable, headstrong, and hurtful behaviors have distinctive predictions. *J Am Acad Child Adolesc Psychiatry*. 2009 Apr; 48(4):404–412. 2009. [PubMed: 19318881]
31. Stringaris A, Goodman R. Three dimensions of oppositionality in youth. *J Child Psychol Psychiatry*. 2009; 50(3):216–223. [PubMed: 19166573]
32. [Accessed Aug 1, 2011] DSM-5 Childhood and Adolescent Disorders Work Group. Justification for Temper Dysregulation Disorder with Dysphoria. <http://dsm5.org/Proposed%20Revision%20Attachments/Justification%20for%20Temper%20Dysregulation%20Disorder%20with%20Dysphoria.pdf>.
33. Copeland WE, Angold A, Costello EJ, Egger H. Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. *Am J Psychiatry*. 2013 Feb 1; 170(2):173–179. [PubMed: 23377638]
34. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry*. 2005 Sep; 44(9):846–871. [PubMed: 16113615]
35. Birmaher B, Axelson D, Monk K, et al. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. *Arch Gen Psychiatry*. 2009 Mar; 66(3):287–296. [PubMed: 19255378]
36. Axelson D, Findling RL, Fristad MA, et al. Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the Longitudinal Assessment of Manic Symptoms study. *J Clin Psychiatry*. 2012 Oct; 73(10):1342–1350. [PubMed: 23140653]
37. Birmaher B, Axelson D, Goldstein B, et al. Psychiatric disorders in preschool offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring Study (BIOS). *Am J Psychiatry*. 2010 Mar; 167(3):321–330. [PubMed: 20080982]
38. Goldstein BI, Shamseddeen W, Axelson DA, et al. Clinical, demographic, and familial correlates of bipolar spectrum disorders among offspring of parents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2010 Apr; 49(4):388–396. [PubMed: 20410731]
39. Bella T, Goldstein T, Axelson D, et al. Psychosocial functioning in offspring of parents with bipolar disorder. *J Affect Disord*. 2011 Sep; 133(1–2):204–211. [PubMed: 21463899]
40. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Arch Gen Psychiatry*. 1992 Aug; 49(8):624–629. [PubMed: 1637252]
41. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997 Jul; 36(7):980–988. [PubMed: 9204677]
42. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*. 2006 Oct; 63(10):1139–1148. [PubMed: 17015816]
43. Birmaher B, Axelson D, Goldstein B, et al. 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 Jul; 166(7):795–804. [PubMed: 19448190]
44. Hollingshead, A. Four Factor Index of Social Status. New Haven: Yale University; 1975.
45. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry*. 1983 Nov; 40(11):1228–1231. [PubMed: 6639293]
46. Diler RS, Birmaher B, Axelson D, et al. Dimensional psychopathology in offspring of parents with bipolar disorder. *Bipolar Disord*. 2011 Nov-Dec; 13(7–8):670–678. [PubMed: 22085480]
47. Dickstein DP, Towbin KE, Van Der Veen JW, et al. Randomized double-blind placebo-controlled trial of lithium in youths with severe mood dysregulation. *J Child Adolesc Psychopharmacol*. 2009 Feb; 19(1):61–73. [PubMed: 19232024]
48. Krieger FV, Pheula GF, Coelho R, et al. An open-label trial of risperidone in children and adolescents with severe mood dysregulation. *J Child Adolesc Psychopharmacol*. 2011 Jun; 21(3): 237–243. [PubMed: 21663426]

Table 1

Estimates of Risk for DMDD Offspring of Parents with Bipolar Disorder (BD) vs. Offspring of Control Parents

	OR	p	95% CI
<i>Univariate analysis</i>			
Parent with BD	8.3	0.005	1.9–36.0
<i>Controlling for demographics and parental diagnoses^a</i>			
Parent with BD	5.4	0.028	1.2–24.5
Parent with ADHD	3.7	0.003	1.6–8.7

Note: ADHD = attention-deficit/hyperactivity disorder

^a All factors $p > 0.10$ removed by backward model selection procedures (age, gender, race, socioeconomic status, living status; parent with depressive disorder, anxiety disorder, oppositional-defiant disorder/conduct disorder, substance use disorder).

Table 2

Comparison of Offspring of Parents with Bipolar Disorder, with or without Disruptive Mood Dysregulation Disorder (DMDD)

	DMDD (+) (N=25)		DMDD (-) (N=350)		Comparison	
	Mean (SD)	N	Mean (SD)	N	T	p
Demographics						
Age	10.5 (2.9)		11.7 (3.4)		1.7	NS
SES	30.9 (13.0)		33.8 (13.9)		1.0	NS
		N		%	X ²	p
Gender (female)	13	52.0	171	48.9	0.92	NS
Race (non-white)	5	20.0	67	19.1	FET	NS
Not living with both biological parents	16	64.0	201	57.6	0.39	NS
<i>Proband parent diagnoses</i>						
Anxiety	21	84.0	260	74.3	1.2	NS
ADHD	14	56.0	85	24.3	12.1	<0.0005
ODD/CD	13	52.0	121	34.6	3.1	NS
SUD	20	80.0	216	61.7	3.4	NS
<i>Offspring diagnoses</i>						
Any depression	8	32.0	33	9.4	FET	0.003
MDD	3	12.0	31	8.9	FET	NS
Dysthymia	5	20.0	2	0.6	FET	<0.0005
Anxiety	6	24.0	89	25.4	0.25	NS
ADHD	15	60.0	78	22.3	17.8	<0.0005
ODD/CD	24	96.0	48	13.7	FET	<0.0005
ODD	16	64.0	42	12.0	FET	<0.0005
CD	8	32.0	6	1.7	FET	<0.0005
ADHD+ODD	8	32.0	24	6.9	FET	<0.0005
ADHD+CD	7	28.0	2	0.6	FET	<0.0005
<i>Global functioning</i>						
	Mean (SD)	Mean (SD)	T	p		

	DMDD (+) (N=25)	DMDD (-) (N=350)	Comparison
Current C-GAS	58.7 (8.4)	75.4 (12.9)	9.1 <0.0005

Note: ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; C-GAS = Children's Global Assessment Scale; FET = Fisher's exact test; NS = not significant; ODD = oppositional defiant disorder; SES = socioeconomic status; SUD = substance use disorder.

Table 3

Estimates of risk for Disruptive Mood Dysregulation Disorder in Offspring of Parents with Bipolar Disorder, by Offspring Diagnosis

	OR	p	95% CI
Any depression	2.4	0.082	0.9–6.3
ADHD 3.1		0.020	1.2–8.2
CD 18.8		<0.005	4.9–71.3

Note: All factors $p > 0.10$ removed by backward model selection procedures (offspring anxiety disorder). ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder.

Table 4
 Chronic Irritability Phenotype in Offspring of Parents with Bipolar Disorder (BD), by Offspring Diagnosis

<i>Offspring diagnoses</i>	(+) Chronic Irritability Phenotype (n=47)		(-) Chronic Irritability Phenotype (n=328)		Comparison	
	N	%	N	%	X ²	p
Any BD	10	21.3	23	7.0	FET	0.004
BD-I or -II	5	10.6	7	2.1	FET	0.010
BD-NOS	5	10.6	16	4.9	FET	NS
Any depression	13	27.7	28	8.5	15.4	<0.0005
MDD	7	14.9	27	8.2	FET	NS
Dysthymia	6	12.8	1	0.3	FET	<0.0005
Anxiety	14	29.8	81	24.7	0.56	NS
ADHD	23	48.9	70	21.3	16.8	<0.0005
ODD/CD	39	83.0	33	10.1	140.9	<0.0005
ODD	27	57.4	31	9.5	72.4	<0.0005
CD	12	25.5	2	0.6	FET	<0.0005
ADHD+ODD	11	23.4	21	6.4	FET	0.001
ADHD+CD	9	19.1	0	0.0	FET	<0.0005

Note: ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; C-GAS = Children's Global Assessment Scale; FET = Fisher's exact test; NOS = not otherwise specified; NS = not significant; ODD = oppositional defiant disorder; SES = socioeconomic status; SUD = substance use disorder.