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

Garrett M. Sparks, MD, MS, David A. Axelson, MD, Haifeng Yu, MS, Wonho Ha, PhD, Javier Ballester, MD, Rasim S. Diler, MD, Benjamin Goldstein, MD, PhD, Tina Goldstein, PhD, Mary Beth Hickey, BA, Cecile D. Ladouceur, PhD, Kelly Monk, RN, Dara Sakolsky, MD, PhD, Boris Birmaher, MD

Objective: Disruptive mood dysregulation disorder (DMDD) is a new diagnosis in the *DSM-5*. Youth with a family history of bipolar disorder (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, aged 6 to 17 years, of community control parents. We calculated odds ratios using generalized linear mixed models. In addition, 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 were the offspring of community control parents (Odds ratio [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%, $\chi^2 = 18.8$, $p < .005$). Within the offspring of parents with BD, the chronic irritability phenotype was frequently present in offspring with diagnoses of BD, depression, attention-deficit/hyperactivity disorder, and disruptive behavior disorders. **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. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(4):408–416. **Key Words:** bipolar disorder, high risk, offspring, familial, disruptive mood dysregulation disorder

The relative increase in the diagnosis of pediatric bipolar disorder (BD) over the past 2 decades[1-4] has prompted substantial debate about how a disorder that was 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 BD.[5] 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 experiencing a bipolar spectrum disorder,[6-9] whereas 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, nonepisodic irritability may have substantially lower rates of progression to BD-I or BD-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 20 years of follow-up,[19,20] although there are some limited data to suggest a possible association with later development of BD.[21,22] Another study specifically identifies anxiety rather

than irritability as a later predictor of BD.[23] Severe chronic irritability appears to be a nonspecific aspect of the development of many later diagnoses.[22,24]

To better characterize youth with chronic irritability who might otherwise be assigned a diagnosis of BD,[25] investigators at the National Institute of Mental Health (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 BD.[25] A case-control study found that youth with SMD have much lower rates of familial BD than youth with BD.[27] 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-up.[28]

A new diagnosis, disruptive mood dysregulation disorder (DMDD), was recently included in *DSM-5*,[29] based largely on research on SMD. Criteria for DMDD are similar to those for 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 years, and an ODD diagnosis is excluded with a DMDD diagnosis. The hallmark symptoms of DMDD are recurrent severe temper outbursts in the 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 limited.[32] Post hoc analysis of existing studies, such as a recent analysis of multiple epidemiologic studies,[33] 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 disorder.[34] 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 sample.[35] 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, although 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 BD.[35] As detailed below, the DMDD criteria were modified because at the time of the original study, the existing assessment tools did not include specifically all aspects of the *DSM-5* criteria, although 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 through 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 that this difference would not be accounted for entirely by comorbid, non-BD parental diagnoses. We also compared the demographic and clinical characteristics of offspring of parents with BD who did or did not meet DMDD criteria. In addition, we hypothesized that the chronic irritability phenotype would be common in youth at familial risk for BD with mood and anxiety disorders, ODD, CD, or 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 *DSM-IV* criteria for BD-I or BD-II. Exclusion criteria were 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 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 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., those with mental retardation), all offspring aged 6 through 17 years from each family were included in the study (n = 375 offspring of parents with BD and n = 241 offspring of control parents), with a single exception described below.

Procedures

After receiving institutional review board approval and after 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 BD-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 degree–level or Master's degree–level interviewers completed all assessments after intensive training for all instruments and after 80% or greater 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 blinded to the psychiatric status of the parents.

SES was ascertained using the Hollingshead scale.[44] 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 the instruments used did not ascertain specifically all of the criteria for the disorder, although the cardinal symptoms of most interest were 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 to 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 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 years (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 SMD[28] 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 because of unclear age of onset and duration.

Chronic Irritability Phenotype

In the secondary analysis, we specifically focused on the DMDD symptom criteria A through 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 through D (regardless of whether they met full DMDD criteria). The DMDD criteria A through 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 that 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. OR 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/ethnicity, 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 $p > .10$ 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 the diagnostic overlap between DMDD and ODD, offspring ODD was not included in the final multivariate model.

RESULTS

DMDD in Offspring of Parents With BD Versus Offspring of Community Controls

Offspring of parents with BD were significantly more likely to meet criteria for DMDD than were offspring of community control parents ($\chi^2 = 11.9$, $p = .001$). In all, 25 (6.7%) offspring of parents with BD met criteria for DMDD (mean age 10.5 years, range 6.5–17.5 years, 13 of 25 subjects female), whereas only 2 offspring (0.8%) of community control parents met criteria for DMDD. There were no statistically significant demographic differences between the 2 groups.

In a univariate model, having a parent with BD was associated with an 8-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 $p > .10$, 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 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 $p < .05$) than their non-DMDD peers. Depressive disorders were more common in offspring with DMDD, although there were only 3 offspring (12.0%) with DMDD and MDD, compared to 31 (8.9%) without DMDD. There were no significant group differences in rates of

TABLE 1 Estimates of Risk for Disruptive Mood Dysregulation Disorder

Offspring of Parents With Bipolar Disorder (BD) vs. Offspring of Control Parents	OR	p	95% CI
Univariate analysis			
Parent with BD	8.3	0.005	1.9-36.0
Controlling for demographics and parental diagnoses[a]			
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; DMDD = disruptive mood dysregulation disorder; OR = odds ratio.

[a]*All factors p > .10 removed by backward model selection procedures (age, gender, race/ethnicity, 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	
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**t**	***p***
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	**%**	**n**	**%**	**χ^2**	***p***
Gender (female)	13	52.0	171	48.9	0.92	NS
Race/ethnicity (nonwhite)	5	20.0	67	19.1	FET	NS
Not living with both biological parents	16	64.0	201	57.6	0.39	NS
Proband parent diagnosis						
Anxiety	21	84.0	260	74.3	1.2	NS
ADHD	14	56.0	85	24.3	12.1	<.0005
ODD/CD	13	52.0	121	34.6	3.1	NS
SUD	20	80.0	216	61.7	3.4	NS
Offspring diagnosis						
Any depression	8	32.0	33	9.4	FET	.003
MDD	3	12.0	31	8.9	FET	NS
Dysthymia	5	20.0	2	0.6	FET	<.0005
Anxiety	6	24.0	89	25.4	0.25	NS
ADHD	15	60.0	78	22.3	17.8	<.0005
ODD/CD	24	96.0	48	13.7	FET	<.0005
ODD	16	64.0	42	12.0	FET	<.0005
CD	8	32.0	6	1.7	FET	<.0005
ADHD+ODD	8	32.0	24	6.9	FET	<.0005
ADHD+CD	7	28.0	2	0.6	FET	<.0005
Global functioning						
	Mean	**SD**	**Mean**	**SD**	**t**	***p***
Current C-GAS	58.7	8.4	75.4	12.9	9.1	<.0005

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

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 criteria for either CD (8 of 25) or ODD (16 of 25). If CD were not applied as an exclusion criteria for ODD, then 23 of 25 met criteria for ODD, with only 1 subject meeting criteria for CD but not ODD.

In addition, DMDD substantially overlapped with ADHD comorbid with either ODD or CD, as 8 of 25 of the offspring with DMDD had comorbid ADHD and ODD, and an additional 7 of 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 20-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, $p = .082$).

Chronic Irritability Phenotype in Offspring of Parents With BD Versus Offspring of Community Controls

Offspring of parents with BD were much more likely to display the chronic irritability phenotype ($\chi^2 = 18.8$, $p < .005$). In all, 47 of 375 offspring (12.5%) of parents with BD displayed the chronic irritability phenotype, whereas only 6 of 241 offspring (2.5%) of control parents displayed the chronic irritability phenotype.

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

TABLE 3 Estimates of Risk for Disruptive Mood Dysregulation Disorder in Offspring of Parents With Bipolar Disorder, by Offspring Diagnosis

Characteristic	OR	*p*	95% CI
Any depression	2.4	.082	0.9-6.3
ADHD	3.1	.020	1.2-8.2
CD	18.8	<.005	4.9-71.3

Note: All factors p > .10 removed by backward model selection procedures (offspring anxiety disorder). ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; OR = odds ratio.

in the offspring of parents with BD (Table 4). The chronic irritability phenotype was commonly present in offspring with any BD (10 of 33, 30.3%), particularly in BD-I or BD-II (5 of 12, 41.7%), any depressive disorder (13 of 41, 31.7%), ADHD (23 of 93, 24.7%), ODD (27 of 58, 46.6%), and CD (12 of 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 8 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% versus 2.5%). As previously reported in this sample,[35] 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 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, and CD were associated with an increased risk of meeting criteria for DMDD, whereas anxiety disorders, contrary to our hypothesis, were not. All but 1 of the youth with DMDD (24 of 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 BD-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-fourth of the offspring with ADHD, one-third of the offspring with BD-I or BD-II, one-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 Study,[28] as well as studies of DMDD in other post hoc studies using 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 1 setting, and 10 met criteria for a BD spectrum disorder. Symptoms occurred only 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 whether 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 1 subject, who was excluded from the analysis. As the ODD supplement is used whenever frequent severe temper outbursts are present, false-negative results 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%) in the study by Copeland *et al.*[33]

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

	(+) Chronic Irritability Phenotype (n=47)		(−) Chronic Irritability Phenotype (n=328)		Comparison	
Offspring diagnosis	**n**	**%**	**N**	**%**	χ^2	***p***
Any BD	10	21.3	23	7.0	FET	.004
BD-I or BD-II	5	10.6	7	2.1	FET	.010
BD-NOS	5	10.6	16	4.9	FET	NS
Any depression	13	27.7	28	8.5	15.4	<.0005
MDD	7	14.9	27	8.2	FET	NS
Dysthymia	6	12.8	1	0.3	FET	<.0005
Anxiety	14	29.8	81	24.7	0.56	NS
ADHD	23	48.9	70	21.3	16.8	<.0005
ODD/CD	39	83.0	33	10.1	140.9	<.0005
ODD	27	57.4	31	9.5	72.4	<.0005
CD	12	25.5	2	0.6	FET	<.0005
ADHD+ODD	11	23.4	21	6.4	FET	.001
ADHD+CD	9	19.1	0	0.0	FET	<.0005

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

Because of our sample size, we were unable to draw conclusions about offspring of control parents who met criteria for DMDD. The findings from 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, whereas 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 symptoms.[32] In this study, about one-third of the offspring with BD displayed chronic irritability and frequent temper outbursts, although 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. Although 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 1 of the offspring of parents with BD who met DMDD criteria would meet criteria for ODD or CD as well (although 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 to 18 years, Diler *et al.*[46] 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 (e.g., impulsivity, irritability, temper outbursts). 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 BD,[16]

and had low rates of familial BD.[27] 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 for developing BD in the future. Several hypotheses could be generated. First, the absence of distinct hypomania or mania episodes at the 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 chronic irritability before 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 BD 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 with a variety of disorders. As investigations increasingly move away from categorical diagnoses toward basic domains of functioning, we will learn the degree to which emotional dysregulation is similar or dissimilar across the diagnostic categories that we currently use to conceptualize our patients.

A diagnosis of DMDD may have a substantial impact on future treatment recommendations, although at this time there are limited data available to directly inform treatment of DMDD. A small study of lithium (n = 14) versus placebo (n = 11) was ineffective for treatment of SMD,[47] whereas a small (n = 21) open-label trial showed that risperidone reduced irritability in SMD.[48] 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 BD,[16] only 1 participant with SMD experienced a manic or hypomanic episode after a 2-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. &

Accepted January 16, 2014.

Drs. Sparks, Axelson, Ha, Ballester, Diler, T. Goldstein, Ladouceur, Sakolsky, and Birmaher, and Mr. Yu, Ms. Hickey, and Ms. Monk are with Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine. Dr. B. Goldstein is with Sunnybrook Health Sciences Centre, University of Toronto.

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

Wonho Ha, PhD, and Haifeng Yu, MS, served as statistical experts for this study.

The authors thank the families for their participation and Melissa Cade, BS, University of Pittsburgh, School of Medicine, for her administrative support.

In loving memory of Sarah Elizabeth Wolfe, MD, MPH.

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 NIMH. 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. 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.

Correspondence to Garrett M. Sparks, MD, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Bellefield Towers, Room 605, Pittsburgh, PA 15213; e-mail: sparksgm@upmc.edu

0890-8567/$36.00/©2014 American Academy of Child and Adolescent Psychiatry

http://dx.doi.org/10.1016/j.jaac.2013.12.026

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