Journal of Child and Adolescent Psychopharmacology

Journal of Child and Adolescent Psychopharmacology Manuscript Central:
http://mc.manuscriptcentral.com/jcap

Disruptive Mood Dysregulation Disorder and Bipolar Disorder Non-Specified: Identical or Fraternal Twins?

Journal:	*Journal of Child and Adolescent Psychopharmacology*
Manuscript ID:	CAP-2015-0062.R1
Manuscript Type:	Original Research
Date Submitted by the Author:	21-May-2015
Complete List of Authors:	FRISTAD, MARY; PROFESSOR OF PSYCHIATRY and PSYCHOLOGY, DIRECTOR, RESEARCH and PSYCHOLOGICAL SERVICES Wolfson, Hannah; The Ohio State University, Psychiatry Algorta, Guillermo; Lancaster University, Division of Health Research Youngstrom, Eric; University of North Carolina, Psychology Arnold, L.; Ohio State University, Psychiatry; Birmaher, Boris; University of Pittsburgh Medical Center, Psychiatry; Horwitz, Sarah; New York University School of Medicine, Child and Adolescent Psychiatry Axelson, David; Ohio State University, Psychiatry; Nationwide Children's Hospital, Child and Adolescent Psychiatry Kowatch, Robert; Ohio State University, Psychiatry; Nationwide Children's Hospital, Child and Adolescent Psychiatry Findling, Robert; Bloomberg Children's Center, Division of Child & Adolescent Psychiatry
Keyword:	Bipolar Disorders, Other Disorders
Abstract:	Objective: To examine similarities and differences between disruptive mood dysregulation disorder (DMDD) and bipolar disorder-not otherwise specified (BP-NOS) in baseline socio-demographic and clinical characteristics and 36-month course of irritability in children aged 6-12.9. Methods: 140 children with DMDD and 77 children with BP-NOS from the Longitudinal Assessment of Manic Symptoms cohort were assessed at baseline, then reassessed every six months for 36 months. Results: Groups were similar on most socio-demographic and baseline clinical variables other than unfiltered (i.e., interviewer-rated regardless of occurrence during a mood episode) Young Mania Rating Scale (YMRS) items. Children with DMDD received lower scores on every item (including irritability) except impaired insight; differences were significant except sexual interest and disruptive-aggressive behavior. Youth with DMDD were significantly less likely to have a biological parent with a bipolar diagnosis compared to youth with BP-NOS. Children with DMDD were more likely to be male and older than children with BP-NOS, both small effect sizes, but had nearly double the rate of disruptive behavior disorders (large effect). Caregiver ratings of irritability based on the Child and Adolescent Symptom

For Peer Review Only

	Inventory-4R (CASI-4R) were comparable at baseline, the DMDD group had a small but significantly steeper decline in scores over 36 months relative to the BP-NOS group (b =-.24, se = .12, 95% CI -.48 to -.0004). Trajectories for both groups were fairly stable, in the mid-range of possible scores. Conclusion: In a sample selected for elevated symptoms of mania, twice as many children were diagnosed with DMDD than BP-NOS. Children with DMDD and BP-NOS are similar on most characteristics other than manic symptoms, per se, and parental history of bipolar disorder. Chronic irritability is common in both groups. Comprehensive evaluations are needed to diagnose appropriately. Clinicians should not assume that chronic irritability leads exclusively to a DMDD diagnosis.

SCHOLARONE™
Manuscripts

For Review Only/Not for Distribution

Disclosures: Dr. Fristad receives royalties from American Psychiatric Press, Guilford Press and Child & Family Psychological Services. Dr. Arnold has received research funding from Curemark, Forest, Lilly, Neuropharm, Novartis, Noven, Shire, and YoungLiving (as well as NIH and Autism Speaks) and has consulted with or been on advisory boards for Gowlings, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Roche, Seaside Therapeutics, Sigma Tau, Shire, and Tris Pharma. Dr. Youngstrom has received grant funding from NIMH and consulted with Otsuka and Lundbeck about assessment. Dr. Birmaher receives or has received royalties from NIMH grants and Random House. Dr. Kowatch has acted and/or served as faculty for REACH Institute, editor for Current Psychiatry, on the DSMB for Forest Pharm, and is employed by The Ohio State University. Dr. Findling receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Alcobra, American Academy of Child & Adolescent Psychiatry, American Physician Institute, American Psychiatric Press, AstraZeneca, Bracket, Bristol-Myers Squibb, CogCubed, Cognition Group, Coronado Biosciences, Dana Foundation, Elsevier, Forest, GlaxoSmithKline, Guilford Press, Johns Hopkins University Press, Johnson and Johnson, Jubilant Clinsys, KemPharm, Lilly, Lundbeck, Merck, NIH, Neurim, Novartis, Noven, Otsuka, Oxford University Press, Pfizer, Physicians Postgraduate Press, Purdue, Rhodes Pharmaceuticals, Roche, Sage, Shire, Sunovion, Supernus Pharmaceuticals, Transcept Pharmaceuticals, Validus, and WebMD. Dr. Frazier has received federal funding or research support from, acted as a consultant to, received travel support from, and/or received a speaker's honorarium from the Cole Family Research Fund, Simons Foundation, Ingalls Foundation, Forest Laboratories, Ecoeos, IntegraGen, Kugona LLC, Shire Development, Bristol-Myers Squibb, National Institutes of Health, and the Brain and Behavior Research Foundation. Hannah Wolfson, Dr. Algorta, Dr. Axelson, Dr. Holland, Dr. Horwitz, Dr. Phillips and Dr. Taylor have no conflicts to declare.

For Peer Review Only Not for Distribution

For Peer Review Only/Not for Publication

Running Head: DMDD & BP-NOS: Similarities and Differences

Disruptive Mood Dysregulation Disorder and Bipolar Disorder Non-Specified: Fraternal or Identical Twins?

Mary A. Fristad, Ph.D. [a]

Hannah Wolfson, B.A. [a]

Guillermo Perez Algorta, Ph.D. [b]

Eric A. Youngstrom, Ph.D. [c]

L. Eugene Arnold, M.D., M. Ed. [a]

Boris Birmaher, M.D. [d]

Sarah Horwitz, Ph.D. [e]

David Axelson, M.D. [a, f]

Robert A. Kowatch, M.D., Ph.D. [a, f]

Robert L. Findling, M.D., M.B.A. [g]

a. Department of Psychiatry and Behavioral Health, The Ohio State University Wexner Medical Center, Columbus, OH
b. Division of Health Research, Lancaster University, Lancaster UK
c. Department of Psychology, University of North Carolina, Chapel Hill, NC
d. Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, PA
e. Department of Child and Adolescent Psychiatry, New York University School of Medicine, New York, NY
f. Section of Child and Adolescent Psychiatry, Nationwide Children's Hospital, Columbus, OH
g. Department of Psychiatry, Johns Hopkins Children's Center/ Kennedy Krieger Institute, Baltimore, MD

And the LAMS Group (Drs. Frazier, Holland, Phillips, Taylor)

Mailing Address: Mary A. Fristad, Ph.D.
Department of Psychiatry and Behavioral Health
The Ohio State University
1670 Upham Drive Suite 460G
Columbus, OH 43210-1250
Email: mary.fristad@osumc.edu
614-293-4572 office, 614-293-4949 fax

Support for this manuscript was provided by the National Institute of Mental Health: R01 MH073801, R01-MH073967, R01-MH073953, R01-MH073816. ~~Support for this manuscript was provided through: NIMH R01 MH073801~~

For Peer Review Only/Not for Publication

For Peer Review Only/Not for Publication

For Peer Review Only/Not for Publication

Abstract

Objective: To examine similarities and differences between disruptive mood dysregulation disorder (DMDD) and bipolar disorder-not otherwise specified (BP-NOS) in baseline socio-demographic and clinical characteristics and 36-month course of irritability in children aged 6-12.9. **Methods:** 140 children with DMDD and 77 children with BP-NOS from the Longitudinal Assessment of Manic Symptoms cohort were assessed at baseline, then reassessed every six months for 36 months. **Results:** Groups were similar on most socio-demographic and baseline clinical variables other than unfiltered (i.e., interviewer-rated regardless of occurrence during a mood episode) Young Mania Rating Scale (YMRS) items. Children with DMDD received lower scores on every item (including irritability) except impaired insight; differences were significant except sexual interest and disruptive-aggressive behavior. Youth with DMDD were significantly less likely to have a biological parent with a bipolar diagnosis compared to youth with BP-NOS. Children with DMDD were more likely to be male and older than children with BP-NOS, both small effect sizes, but had nearly double the rate of disruptive behavior disorders (large effect). Caregiver ratings of irritability based on the Child and Adolescent Symptom Inventory-4R (CASI-4R) were comparable at baseline, ~~did not differ significantly between the two groups over the 36 month~~the DMDD group had a small but significantly steeper decline in scores over 36 months relative to the BP-NOS group ~~follow up period, with a significant but small difference in slopes further reducing any initial differences~~ (b =-.24, se = .12, *95% CI* -.48 to -.0004). Trajectories for both groups were fairly stable, in the mid-range of possible scores. **Conclusion:** In a sample selected for elevated symptoms of mania, twice as many children were diagnosed with DMDD than BP-NOS. Children with DMDD and BP-NOS are similar on most characteristics other than manic symptoms, per se, and parental history of bipolar disorder.

Chronic irritability is common in both groups. Comprehensive evaluations are needed to diagnose appropriately. Clinicians should not assume that chronic irritability leads exclusively to a DMDD diagnosis.

Keywords: DMDD, BP-NOS, longitudinal, phenomenology

For Peer Review Only/Not for Publication

Disruptive Mood Dysregulation Disorder and Bipolar Disorder Not Otherwise Specified: Fraternal or Identical Twins?

Disruptive mood dysregulation disorder (DMDD) was added to the *DSM-5* in large part to decrease the over-diagnosis of bipolar spectrum disorders (BPSD), including bipolar disorder not-otherwise-specified (BP-NOS; in DSM-5, this diagnosis is incorporated into Other Specified Bipolar and Related Disorders, or OSBARD) (American Psychiatric Association 2013). Although temper outbursts and irritability are common symptoms in youth presenting to outpatient clinics, by definition, DMDD is characterized by persistent, non-episodic irritability and/or anger that go far beyond the severity and frequency of typical temper tantrums, with symptoms occurring persistently over at least one year (American Psychiatric Association 2013). Additionally, by definition, youth with DMDD maintain an irritable and/or angry mood between outbursts, whereas youth with BP-NOS may return to a euthymic state and are more likely to show spontaneous fluctuations or episodes (Findling, Kowatch, & Post, 2003)(Leibenluft, 2011; E A Youngstrom, Birmaher, & Findling, 2008).

Previous studies examined a precursor to DMDD called severe mood dysregulation (SMD; Leibenluft, 2011). Towbin and colleagues (2013) summarized the similarities and differences between SMD and BP-NOS based on their respective definitions. Chronic irritability is required for SMD and allowable, but not required for BP-NOS. A history of distinct, recurrent manic or hypomanic episodes that are too brief in duration (typically two to three days) to meet criteria for bipolar disorder type I or II are exclusionary for SMD but required for BP-NOS. A family history of bipolar disorder and the likelihood of converting to bipolar disorder type I or II

For Peer Review Only/Not for Publication

within seven years is unlikely for SMD but is true for approximately half of those with BP-NOS. A history of a full duration manic episode is exclusionary for both SMD and BP-NOS, as is a history of hypomania. (For the BP-NOS group, this is only true if there is also a history of MDD, which would lead to a diagnosis of bipolar disorder type II.) However, empirical comparison of these two diagnoses is quite limited.

The majority of research conducted on SMD has used data collected from a highly selected sample from the National Institute of Mental Health (NIMH) Intramural Program. Within a sample of 146 youth who met the SMD phenotype, the majority were male (66%) and had elevated rates of ADHD (86%), oppositional defiant disorder (ODD) (85%) and anxiety disorders (58%) (Leibenluft 2011). Although SMD includes the main criteria of DMDD, it also requires symptoms of hyperarousal similar to those of attention-deficit/hyperactivity disorder (ADHD) (Leibenluft et al. 2003). While some research suggests similarities between SMD/DMDD and bipolar disorder, such as deficits in facial emotion labeling (Guyer et al. 2007), differences are more common. In an epidemiologic examination of parental psychiatric history, parents of youth with SMD were significantly less likely to be diagnosed with a BPSD than parents of youth with a BPSD (2.7% versus 33.3%) (Brotman et al. 2007). Stringaris and colleagues (2010) examined the longitudinal course of this cohort and reported the children with SMD were 50 times less likely to develop a (hypo-)manic or mixed episode compared to youth with bipolar disorder.

According to a community-based follow-up study, SMD has a lifetime prevalence of 3.3% in youth aged 9 to 19; at an eight-year follow-up, youth diagnosed with SMD at an average age of 10 were significantly more likely than those not diagnosed with SMD to have a depressive disorder by age 18 (odds ratio 7.2, confidence interval 1.3-38.8, $p = .02$) but not bipolar disorder

For Peer Review Only/Not for Publication

(Brotman et al. 2006). Of note, of those participants without SMD, a quarter had other diagnoses, including any emotional disorder, 6.1%, any behavioral disorder, 19.6%, any anxiety disorder, 4.5% or substance abuse/dependence, 8.8% (Brotman et al. 2006). Copeland and colleagues (2014) followed this cohort into adulthood. Those with SMD (using retrofitted criteria to meet DMDD criteria by these authors) were significantly more likely than those without SMD/DMDD to have an adult depressive or anxiety disorder and they had a 10.3 greater odds of having multiple adult disorders than those without SMD/DMDD (Copeland et al. 2014). The authors did not report on presence/absence of bipolar disorder, so it is unknown if rates differed in adulthood between participants who did versus did not meet criteria for SMD/DMDD as children.

A small number of studies have characterized DMDD. Within a large community sample of 6-year-old children, 8% met criteria for DMDD when criteria were retrospectively applied. Of these, 61% demonstrated comorbidity with an emotional or behavioral disorder (Dougherty et al. 2014). Participants with DMDD had significantly higher rates of oppositional defiant disorder and depression than participants without DMDD (55% vs 5%, 13% vs 5%, respectively) (Dougherty et al. 2014). Both ODD and ADHD at 3 years of age predicted DMDD at age 6 (Dougherty et al. 2014). Familial and environmental predictors included low parental support, lower levels of marital satisfaction, and parental lifetime substance use disorders. However, parental internalizing disorders were not associated with a DMDD diagnosis at age 6 (Dougherty et al. 2014).

Axelson et al. (2012) utilized the Longitudinal Assessment of Manic Symptoms (LAMS) sample to characterize children who met all DSM-5 DMDD criteria, with the exception being that participants with BPSD were allowed in the DMDD group. Just over one-fourth (26%) of the LAMS sample met DMDD criteria at baseline. Results indicated significantly higher rates of

For Peer Review Only/Not for Publication

ADHD (79%), disruptive behavior disorders (96%; ODD, 78%; conduct disorder, 18%) in children who met DMDD compared to those who did not meet criteria for DMDD. In addition, youth with DMDD had significantly elevated scores on dimensional measures of mania and depression, and were more impaired than those without DMDD.

Sparks and colleagues (2014) examined offspring of parents who had bipolar disorder. They reported that these offspring were more likely than offspring of community control parents to meet DMDD criteria (odds ratio 8.3, 6.7% versus 0.8%) and to have higher rates of chronic irritability (12.5% versus 2.5%, $p < .005$). Chronic irritability was noted in offspring who had diagnoses of bipolar disorder, depression, ADHD and disruptive behavior disorders.

Margulies and colleagues (2014) examined rates of DMDD in 82 consecutive psychiatrically hospitalized children. They reported that nearly one-third (31%) of children met DMDD criteria by parental report; however, only half of these (16%) did when diagnosis was based on inpatient observation. Over half (56%) of the 82 children had parent-reported manic symptoms (scores ≥20 on the Child Mania Rating Scale-Parent form). Of these 46, nearly half (n=21; 46%) met DMDD by parental report but only one-third (17.4%) did based on inpatient observation. The authors conclude "The overall utility of the DMDD diagnosis and whether it would prevent children from receiving other and better-defined diagnoses remains to be seen." (p. 495).

To date, no one has compared DMDD directly to BP-NOS to determine the similarities and differences between these two diagnoses over time. Cross-sectionally, of course, the two diagnoses are expected to exhibit similarities (and therefore, the new diagnosis of DMDD is intended to decrease the misdiagnosis of bipolar disorder), but their longitudinal courses are expected to differ. This is important as treatment, particularly pharmacologic interventions, likely

For Peer Review Only/Not for Publication

will differ for these two diagnoses. If DMDD develops into depressive and/or anxiety disorders, anti-depressant treatment would be a logical first pharmacologic treatment of choice. Alternately, if DMDD continues to show a more externalizing behavior trajectory--consistent with the overlap in symptoms with oppositional-defiant disorder (Axelson et al. 2011) and the cross-sectional comorbidities with disruptive behavior disorders noted above – then a different treatment package of psychosocial (Eyberg, Nelson, & Boggs, 2008) and pharmacological interventions would be indicated (Jensen et al. 2007). In contrast, if BP-NOS continues to express itself as part of the bipolar continuum, atypical antipsychotics and/or mood stabilizers likely would be the first pharmacologic treatment of choice (McClellan, Kowatch, & Findling, 2007). Thus, it is crucial to develop clear templates for clinicians so they can precisely differentiate youth with DMDD from youth with BP-NOS.

This study used a longitudinal cohort to compare children who met diagnostic criteria for DMDD or BP-NOS at entry into the study. First, we determined whether the two groups differed on a variety of socio-demographic and clinical variables. Second, we evaluated group differences in participants' parent-rated irritability over a 36 month follow-up period. We hypothesized that youth with DMDD and BP-NOS would have many similarities on symptoms common in outpatient clinics (e.g., irritability, aggression, impulsivity) but that children with DMDD versus BP-NOS would differ, by definition, in their expression of classically manic symptoms (e.g., euphoric mood, decreased sleep). Further, given the diagnostic criteria for DMDD, the two groups should exhibit distinct irritability trajectories, with DMDD participants maintaining consistently higher levels of irritability than youth with BP-NOS, whose irritability should be largely confined to episodes.

Method

For Peer Review Only/Not for Publication

Ascertainment of this sample has been described in detail elsewhere (Horwitz et al, 2010; Findling et al, 2010). In summary, institutional review boards at each university-affiliated LAMS sites (Case Western Reserve University, Cincinnati Children's Medical Center, the Ohio State University, and the University of Pittsburgh Medical Center) approved all procedures. Parents/guardians at outpatient clinics provided written informed consent before completing the screening procedure, which consisted of a brief demographic form and the PGBI-10M (Youngstrom et al. 2008) to screen for elevated symptoms of mania (ESM). Results from this screening were used to invite a group of ESM+ children and a smaller, demographically matched sample of ESM- children to enroll into the longitudinal portion of the study, for which parents provided consent and the children, assent prior to their participation.

Sample

A subsample of 217 children aged 6 to 12.9 years from the LAMS cohort (N=685) were included in the current study on the basis of a BP-NOS (n=77) or DMDD (n=140) diagnosis (defined below) at baseline. In youth from the original cohort, the diagnoses most commonly assigned at baseline were: ADHD (76.1%), other disruptive behavior disorders (51.1%), bipolar spectrum disorders (22.9%), depressive disorders (17.5%) and anxiety disorders (31.3%) (Findling et al. 2010).

Measures

Demographics. Parents/guardians provided information including age, sex, race, ethnicity, and health insurance status.

Family History. The Family History Screen (Weissman et al. 2000) was completed to collect information on parental psychiatric disorders. In addition to presence or absence of manic symptoms, parents were considered to have a probable bipolar disorder if they had elated mood

For Peer Review Only/Not for Publication

For Peer Review Only/Not for Publication

plus three additional symptoms of mania or irritable mood plus four additional symptoms of mania.

Psychiatric Diagnoses. Trained interviewers administered to children and their parent or legal guardian the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL), with additional items about depressive and manic symptoms from the Washington University St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL-W) (Kaufman et al. 1997; Geller et al. 2001). Additional questions were added to screen for pervasive developmental disorders. Study interviewers completed this semi-structured interview to assess current and lifetime psychiatric diagnoses and the duration of each illness. Mood disorder diagnoses were evaluated at the baseline assessment and every six months afterwards.

DMDD Diagnosis. DMDD in the LAMS sample was originally operationalized by Axelson et al. (2012) using K-SADS-PL-W items. For this study, we excluded 44 participants with bipolar diagnoses (n=27 who met criteria for DMDD and BP-NOS, these participants were included in the BP-NOS group; n=16, bipolar type 1; n=1, cyclothymic disorder) from the DMDD group to more closely resemble *DSM*-5 criteria (American Psychiatric Association 2013).

- **Severe recurrent temper outbursts.** This criterion was derived from the "loses temper" item (at threshold, frequency is 2-5 times per week).
- **Chronic irritability.** This criterion was derived from the oppositional defiant disorder section of the behavioral disorders supplement: "easily annoyed or angered" and "angry or resentful" items (both at threshold).

- **Duration.** Participants administered the K-SADS-PL-W oppositional defiant disorder supplement were assessed for the presence of symptoms for a least 6 months, regardless of if they met full criteria for oppositional defiant disorder. DMDD criterion states that symptoms must have been present for at least 12 months, with no more than 3 consecutive months when the person was without the preceding diagnostic criteria.
- **Impairment in more than 1 setting.** The oppositional defiant disorder section of the behavioral disorders supplement evaluated impairment in at least 2 settings.
- **No presence of a BPSD diagnosis**. Youth with any bipolar spectrum disorder (i.e., bipolar I or II disorder, BP-NOS, cyclothymia) were excluded.

BP-NOS Diagnosis. The LAMS study uses previously developed criteria from the Course and Outcomes of Bipolar Youth (COBY) study to diagnose BP-NOS (Birmaher et al, 2009). These are:

- Child does not meet the DSM-IV criteria for bipolar disorder type I or II
- A distinct period of abnormally elevated, expansive, or irritable mood plus the following

  1. 2 DSM-IV-TR B-criterion manic symptoms (3 if the mood is irritability only) that are clearly associated with onset of abnormal mood

  2. A clear change in functioning

  3. Presence of elated and/or irritable mood and manic symptoms for a significant part of the day (4 h, although this does not necessarily need to be expressed consecutively)

For Peer Review Only/Not for Publication

4. 4 days (not necessarily consecutive) meeting criteria B.1eB.3 over patient's lifetime

C. Mood and affective symptoms must be abnormal for child's level of development and environment

- Symptoms or mood changes that occur during substance use or antidepressant treatment do not count toward a bipolar diagnosis
- Exclusion criteria

  1. Current or lifetime DSM-IV diagnosis of schizophrenia, mental retardation, autism, or severe autism spectrum disorders

  2. Mood disorders due to substance abuse, a medical condition, or secondary to use of medications (e.g., corticosteroids)
- If onset occurs prior to onset of comorbid substance use disorders, cases are included
- Children with mild comorbid Asperger disorder or pervasive developmental disorder not otherwise specified are included if their mood symptomatology was clearly episodic and best accounted for by the bipolar diagnosis

Medication History. Parents/guardians provided a comprehensive history of the child's past and current psychotropic medication usage.

Functional Assessment. Study interviewers assigned ratings on the Children's Global Assessment Scale (CGAS) following completion of their comprehensive evaluation to assess the severity of current and lifetime impairment (Shaffer et al. 1983). The CGAS captures children's functionality at home, at school, and with peers.

For Peer Review Only/Not for Publication

For Peer Review Only/Not for Publication

Mood Ratings. Unfiltered (meaning that severity of the symptom was rated regardless of whether it occurred in the context of a mood episode) (Yee et al. 2014) ratings of manic and depressive symptoms that occurred in the past 2 weeks were obtained via interview of the child and parent/guardian using the Young Mania Rating Scale (YMRS) and the Children's Depression Rating Scale- Revised (CDRS-R) (Young et al. 1978; Poznanski et al. 1984). In contrast to methodology used by Axelson et al. (2012), the current study included total scores of irritability items so that scores from the two diagnostic groups in this study could be compared to results from other studies.

Questionnaires. Several self-report measures were completed by caregivers to characterize children's symptoms. Elevated symptoms of mania were assessed using the PGBI-10M (Youngstrom et al. 2008). Anxiety symptoms during the past 6 months were obtained from the Screen for Child Anxiety Related Emotional Disorders (SCARED-P) (Birmaher et al. 1997).

Irritability Scale. An irritability scale was derived from items found in the Child and Adolescent Symptom Inventory-4R (CASI-4R) ADHD, oppositional defiant disorder, and conduct disorder subscales (Gadow and Sprafkin 2005). This was done to generate a continuous irritability variable based on caregiver ~~self-~~report of the child's symptoms. To secure content validity with a previous well-validated irritability scale, Affective Reactivity Index items (Stringaris et al. 2012), were considered in the selection of CASI-4R items. Six items were identified from the CASI-4R that mapped onto the ARI items: 1) loses temper; 2) irritable for most of the day; 3) touchy or easily annoyed; 4) angry or resentful; 5) extremely tense or unable to relax; 6) deliberately annoys others. Principal axis factor analysis confirmed a single factor solution that showed an excellent level of reliability (Cronbach's alpha = 0.87).

Analyses

For Peer Review Only/Not for Publication

Statistical analyses used IBM SPSS version 22.0 (IBM Corp. 2013) and R (R Core Team 2014). Unweighted means, standard deviations, and frequency counts were calculated for descriptive statistics. Between-group differences were assessed with chi square analyses for binary variables and independent t-tests for continuous variables. Cohen's *d* effect size using the pooled standard deviation and *phi*'s for chi-squares were computed.

To compare caregiver-reported irritability level at baseline and during the 36-month follow-up observation between diagnostic groups, a hierarchical linear model, with a random intercept and slope, with repeated measures nested within subject (level 1), and time and diagnostic group as fixed covariates (level 2), was used. The diagnostic group*time interaction was the key outcome, with the coding using DMDD as the target and BP-NOS as the comparison. A model-based (semi) parametric bootstrap method was used to generate 95% confidence intervals based on 10000 bootstrap replicates.

Results

Baseline Comparisons

First, demographic variables were compared between the 140 children who met criteria for DMDD and the 77 who met criteria for BP-NOS. Significant age and sex differences between diagnostic groups were observed (Table 1). Children with DMDD were more likely to be male and younger than children with BP-NOS, with small effect sizes for both factors. There were no significant differences between groups in clinical treatment history. When baseline clinical characteristics were compared, children with DMDD had lower levels of manic symptoms but nearly double the rate of disruptive behavior disorders, with large effect sizes for both factors.

When specific items on the unfiltered (i.e., rated regardless of occurrence within a mood episode) interviewer-rated YMRS were compared, children with DMDD averaged equal or lower

scores on every item except impaired insight; all differences were significant except for sexual interest and disruptive-aggressive behavior (Table 2). Of note, children with DMDD had lower YMRS irritability scores than children with BP-NOS. Participants with DMDD did not significantly differ from those with BP-NOS in presence or absence of any manic symptoms in biological parents. However, participants with DMDD were significantly less likely than those with BP-NOS to have a biological parent with a probable bipolar spectrum diagnosis (19% vs 31%, p<.05).

Longitudinal Comparison

The distribution of scores on the Irritability Scale, which is based on caregiver-report of the child's behavior, was approximately normal for the two groups combined, with no outliers (Figure 1). At baseline, although caregivers of children with DMDD rated them higher on irritability than caregivers of children with BP-NOS, this did not reach statistical significance ~~reports of irritability levels did not differ between the two groups~~ (b =.51, se = .48, t-$test$ = 1.07, p>.05, Table 3). Irritability decreased slightly faster for the DMDD group over the 36 month-follow up period (b =-.24, se = .12, t-$test$ = -1.96, p=.0499). Trajectories for both groups were fairly stable, in the mid-range of possible scores (Figure 2).

As there were 27 children who fulfilled criteria for DMDD (other than the bipolar symptom exclusion) and BP-NOS, we completed one additional post-hoc comparison, comparing rates of irritability between three groups, DMDD+BP-NOS (n=27), DMDD only (n=140) and BP-NOS only (n=50). The DMDD+BP-NOS and DMDD groups had higher levels of caregiver-reported irritability at baseline than the BP-NOS only group. The only significant difference in slopes was between DMDD only and DMDD+BP-NOS, with the latter group showing the slowest decline in irritability (b=0.38, 95% [.02 - .74].

For Peer Review Only/Not for Publication

For Peer Review Only/Not for Publication

Discussion

We evaluated similarities and differences between DMDD and BP-NOS on socio-demographic and clinical variables at baseline, particularly YMRS items, and tested whether rates of caregiver-reported irritability differed between the two groups over time. DMDD was not clearly distinguished from BP-NOS on most comparison points other than YMRS items and rates of a probable bipolar diagnosis in biological parents. Of note, the YMRS was administered in an unfiltered manner (i.e., in a "what you see is what you get" manner regardless of whether the symptoms occurred within the context of a mood episode) and was not used to make the diagnosis of DMDD or BP-NOS (for a further discussion of this, see Yee et al. 2014).

Children with DMDD were younger and more likely to be boys. However, these were not striking differences—average ages for both groups were in the 9 to 10 year old range and boys were the majority of each group. Youth with DMDD were similar to those with BP-NOS on most clinical factors including: number of diagnoses; number of medications; likelihood of prior hospitalization; comorbid ADHD, anxiety disorders, pervasive developmental disorders, elimination disorders, and psychosis; global impairment; PGBI-10M; and depressive and anxiety symptom severity. Only disruptive behavior disorders were more common in children with DMDD, consistent with prior research (Stringaris et al. 2010; Axelson et al. 2012; Towbin et al. 2013). Irritability on the parent-reported Irritability Scale was nominally higher at baseline, but to a non-significant degree, for t~~T~~he DMDD group~~ scored half a point higher than the BP-NOS group on the parent-reported measure of irritability at baseline~~, compared to the BP-NOS group, but then decreased more rapidly ~~by a quarter point per six month interval, erasing the already small difference a year later~~over time. The difference in slopes was statistically significant, but unlikely to be clinically meaningful. The change of a quarter point is miniscule, given that the

scale is only accurate to +/-1.90 points for individual change scores, based on the standard error of the difference score (Jacobson & Truax, 1991).

YMRS total scores and all item scores except impaired insight (which was negligibly different between groups) were similar or lower for children with DMDD compared to children with BP-NOS. Notably, elevated mood, increased motor activity, decreased sleep, pressured speech, impaired language/thought, thought content, and appearance were all more elevated in children with BP-NOS. Even irritability on the YMRS was more severe for children with BP-NOS. ~~when episodic fluctuations and spontaneous changes were included in the definition.~~

Group comparisons of caregiver-reported irritability revealed ~~two~~ three findings of interest. First, the groups did not differ significantly on either the level or change over time in ratings of irritability. While there was a small decrement in irritability scores over time for the DMDD group, irritability remained stable in the BP-NOS group. Second, both groups had mid-range irritability scores of 10-12 on a 0-18 scale that remained fairly consistent over the three years. Although the presence of both DMDD and BP-NOS is disallowed per DSM-5 rules, when the subgroup who met criteria for both diagnoses (other than the manic symptom exclusion for DMDD) was compared on chronic irritability to those children who had DMDD only or BP-NOS only, the DMDD+BP-NOS children had significantly less decline in caregiver-reported irritability over time.

Differences in findings regarding irritability, depending on whether the interviewer rated presence/absence and severity based on a “what you see is what you get” unfiltered manner or whether caregivers reported on their children’s behavior, are interesting. Children with DMDD appeared less impaired than children with BP-NOS using the former strategy, but the two groups appeared similar when using caregiver report on rating scales. Perhaps the frustration of raising a

For Peer Review Only/Not for Publication

child with a disruptive behavior disorder, which were ubiquitous in the DMDD group, leads to higher caregiver reports of irritability, whereas interviewer-based questioning that incorporates parent and child input as well as clinical observation during the interview, puts a greater perspective on the severity of the behaviors and affect observed. This is in keeping with previous research showing much lower rates of DMDD when diagnoses are based on clinical observation rather than parental self-report (Margulies et al., 2014).

DMDD was included in the DSM-5 as a way to decrease diagnoses of BPSD in children. Pharmacologic management, in particular, might differ for children with DMDD compared to those with BP-NOS. Children with DMDD initially display high rates of externalizing symptoms and comorbid disruptive behavior disorders with subsequent risk for development of depressive disorders, which would suggest treatment with antidepressant medications. Those with BP-NOS are likely to be treated with first-line medications for bipolar disorder. Clarifying the differentiating features of DMDD and BP-NOS is therefore crucial for the effective management of these disorders. Results from this study point to cross-sectional similarities between these two diagnostic groups on nearly every feature except more classically manic symptoms and family history of probable bipolar disorder in parents. Further, the trajectory of caregiver-reported irritability over a three year interval does not meaningfully separate the two groups. Thus, it will be important for clinicians not to use caregiver-reported chronic irritability in isolation as a reason to consider DMDD the most appropriate diagnosis, but rather to conduct a thorough review of symptoms and course to determine if a child fulfills DMDD, BP-NOS or other primary and co-morbid diagnoses. In this regard, it is noteworthy that clinicians achieved lower reliability for DMDD than for pediatric bipolar diagnoses in the DSM-5 field trials (Regier et al. 2012). Semi-structured approaches (Rettew, Lynch, Achenbach, Dumenci, & Ivanova, 2009) or

For Peer Review Only/Not for Publication

checklists as a way of augmenting the family's description of the presenting problem could be helpful in improving the reproducibility of diagnoses (Croskerry, 2003; Gawande, 2010; Youngstrom, Choukas-Bradley, Calhoun, & Jensen-Doss, 2014).

Several limitations of this study are important to note. The current study utilized retrofitted K-SADS-PL-W responses to determine DMDD diagnoses. Our criteria slightly modified those previously reported in Axelson et al. (2012) to better align with *DSM*-5 diagnostic criteria. The majority of LAMS study participants were recruited due to their elevated PGBI-10M scores, resulting in a sample with disproportionately elevated symptoms of mania and therefore, not fully representative of clinical outpatient samples. Despite these limitations, these findings suggest that children with DMDD and BP-NOS are very similar on most characteristics other than manic symptoms and a probable bipolar family history. Even in a sample enriched with children who have elevated symptoms of mania, DMDD outnumbers a BP-NOS diagnosis almost 2:1. Clinicians will need to complete comprehensive evaluations to appropriately diagnose children and not assume that caregiver-reported chronic irritability leads exclusively to a DMDD diagnosis. Children with DMDD and BP-NOS are fraternal, not identical twins, but they may easily confuse the casual observer.

For Peer Review Only/Not for Publication

References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2013.

Axelson DA, Birmaher B, Findling RL, Fristad MA, Kowatch RA, Youngstrom EA, Arnold EL, Goldstein BI, Goldstein TR, Chang KD, Delbello MP, Ryan ND, Diler RS: Concerns regarding the inclusion of temper dysregulation disorder with dysphoria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. J Clin Psychiatry 72(9):1257-1262, 2011.

Axelson D, Findling R, Fristad MA, Kowatch RA, Youngstrom EA, Horwitz SM, Arnold E, Frazier TW, Ryan N, Demeter C, Gill MK, Hauser-Harrington JC, Depew J, Kennedy SM, Gron BA, Rowles BM, Birmaher B: Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the Longitudinal Assessment of Manic Symptoms study. J Clin Psychiatry 73(10):1342-1350, 2012.

Birmaher B, Khetarpal S, Brent D, Cully M, Balach L, Kaufman J, Neer SM: The Screen for Child Anxiety Related Emotional Disorders (SCARED): Scale construction and psychometric characteristics. J Am Acad Child Adolesc Psychiatry 36(4):545-553, 1997.

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 C, Goldstein T, Ryan N, Keller M: Four-year

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Indent: Left: 0", First line: 0", Line spacing: Double

For Peer Review Only/Not for Publication

longitudinal course of children and adolescents with bipolar spectrum disorder: The course and outcome of bipolar youth (COBY) study. Am J Psychiatry 166(7):795-804, 2009.

Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, Egger HL, Angold A, Pine DS, Leibenluft E: Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biol Psychiatry 60:991-997, 2006.

Brotman MA, Kassem L, Reising MM, Guyer AE, Dickstein DP, Rich BA, Towbin KE, Pine DS, McMahon FJ, Leibenluft E: Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation. Am J Psychiatry, 164(8):1238-1241, 2007.

Copeland WE, Shanahan L, Egger H, Angold A, Costello EJ: Adult diagnostic and functional outcomes of DSM-5 disruptive mood dysregulation disorder. Am J Psychiatry, 171:668-674, 2014.

Croskerry P: The importance of cognitive errors in diagnosis and strategies to minimize them. Academic Medicine, 78(8):775-780, 2003.

Deveney CM, Hommer RE, Reeves E, Stringaris A, Hinton KE, Haring CT, Vidal-Ribas P, Towbin K, Brotman M, Leibenluft E: A prospective study of severe irritability in youths: 2- and 4-year follow-up. Depression and Anxiety, 00:1-9, 2014.

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

For Peer Review Only/Not for Publication

Dougherty LR, Smith VC, Bufferd SJ, Carlson GA, Stringaris A, Leibenluft E, Klein DN: DSM-5 disruptive mood dysregulation disorder: Correlates and predictors in young children. Psychological Medicine, 44:2339-2350, 2014.

Eyberg SM, Nelson MM & Boggs SR: Evidence-based psychological treatments for children and adolescents with disruptive behavior. Journal of Clinical Child and Adolescent Psychology, 37(1):215-237, 2008.

Findling RL, Kowatch RA, & Post RM: Pediatric bipolar disorder: A handbook for clinicians. London: Martin Dunitz, 2003.

Findling RL, Youngstrom EA, Fristad MA, Birmaher B, Kowatch RA, Arnold LE, Frazier TW, Axelson D, Ryan N, Demeter CA, Fields B, Depew J, Kennedy SM, Marsh L, Rowles BM, Horwitz SM: Characteristics of children with elevated symptoms of mania: the Longitudinal Assessment of Manic Symptoms (LAMS) study. J Clinc Psychiatry, 71(12): 1664-1672, 2010.

Gadow KD, Sprafkin J: Child and Adolescent Symptom Inventory-4R. Checkmate Plus: Stony Brook, NY: 2005.

Gawande, A. The Checklist Manifesto. New York, NY: Penguin. (2010).

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

For Peer Review Only/Not for Publication

Geller B, Zimerman B, Williams M, Bolhofner K, Craney J, DelBello MP, Soutullo C: Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. J Am Acad Child Adolesc Psychiatry 40(4):450-455, 2001.

Guyer AE, McClure EB, Adler AD, Brotman MA, Rich BA, Kime AS, Pine DS, Ermst M, Leibenluft E: Specificity of facial expression labeling deficits in childhood psychopathology. Journal of Child Psychology and Psychiatry, 48(9):863-871, 2007.

Horwitz SM, Demeter CA, Pagano ME, Youngstrom EA, Fristad MA, Arnold LE, Birmaher B, Gill MK, Axelson D, Kowatch RA, Frazier TW, Findling RL: Longitudinal Assessment of Manic Symptoms (LAMS) study: Background, design, and initial screening results. The Journal of Clinical Psychiatry 71(11): 1511-1517, 2010.

IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol, 59, 12-19.

Jensen PS, Youngstrom EA, Steiner H, Findling RL, Meyer RE, Malone RP, Carlson GA, Coccaro EF, Aman MG, Blair J, Dougherty D, Ferris C, Flynn L, Green E, Hoagwood K, Hutchinson J, Laughren T, Leve LD, Novins DK, Vitello B: Consensus report on impulsive

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

For Peer Review Only/Not for Publication

aggression as a symptom across diagnostic categories in child psychiatry: Implications for medication studies. J Am Acad Child Adolesc Psychiatry 46(3):309-322, 2007.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N: 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 36(7): 980-988, 1997.

Leibenluft E, Dennis CS, Towbin KE, Bhangoo RK, Pine DS: Defining clinical phenotypes of juvenile mania. Am J Psychiatry 160(3):430-437, 2003.

Leibenluft E: Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatry 168(2):129-142, 2011.

Margulies DM, Weintraub S, Basile J, Grover PJ, Carlson GA: Will disruptive mood dysregulation disorder reduce false diagnosis of bipolar disorder in children? Bipolar Disorders 14:488-496, 2012.

McClellan J, Kowatch R, & Findling RL: Practice Parameter for the assessment and treatment of children and adolescents with bipolar disorder. Journal of Child & Adolescent Psychiatry 46(1):107-125, 2007.

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

For Peer Review Only/Not for Publication

Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, Gibbons R: Preliminary studies of the reliability and validity of the Children's Depression Rating Scale. Journal of the American Academy of Child Psychiatry 23(2):191-197, 1984.

R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

Rettew DC, Lynch AD, Achenbach TM, Dumenci L, Ivanova MY: Meta-analyses of agreement between diagnoses made from clinical evaluations and standardized diagnostic interviews. International Journal of Methods in Psychiatric Research 18(3):169-184, 2009.

Roy AK, Lopes V, Klein RG: Disruptive Mood Dysregulation Disorder: A new diagnostic approach to chronic irritability in youth. Am J Psychiatry 171:918-924, 2014.

Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S: A Children's Global Assessment Scale (CGAS). Arch Gen Psychiatry 40:1228-1231, 1983.

Sparks GM, Axelson DA, Haifeng Y, Ha W, Ballester J, Diler RS, Goldstein B, Goldstein T, Hickey MB, Ladouceur CD, Monk K, Sakolsky D, Birmaher B: Disruptive mood dysregulation disorder and chronic irritability in youth at familial risk for bipolar disorder. Journal of the American Academy of Child & Adolescent Psychiatry: 53(4):408-416, 2014.

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

For Peer Review Only/Not for Publication

Stringaris A, Cohen P, Pine D, Leibenluft E: Adult outcomes of youth irritability: A 20-year prospective community-based study. Am J Psychiatry 166(9):1048-1054, 2009.

Stringaris A, Baroni A, Haimm C, Brotman M, Lowe CH, Myers F, Rustgi E, Wheeler W, Kayser R, Towbin K, Leibenluft E: Pediatric bipolar disorder versus severe mood dysregulation: Risk for manic episodes on follow-up. Journal of the American Academy of Child and Adolescent Psychiatry 49(4):397-405, 2010.

Stringaris A, Goodman R, Ferdinando S, Razdan V, Muhrer E, Leibenluft E, Brotman M: The Affective Reactivity Index: A concise irritability scale for clinical and research settings. Journal of Child Psychology and Psychiatry 53(11):1109-1117, 2012.

Towbin K, Axelson D, Leibenluft E, Birmaher B: Differentiating bipolar disorder-not otherwise specified and severe mood dysregulation. Journal of the American Academy of Child & Psychiatry 52(5): 466-481, 2013.

Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M: Brief screening for family psychiatric history: The family history screen. Arch Gen Psychiatry 57(7): 675-682, 2000.

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

For Peer Review Only/Not for Publication

Yee AM, Algorta GP, Youngstrom EA, Findling RL, Birmaher B, Fristad MA, The Lams Group: Unfiltered Administration of the YMRS and CDRS-R in a Clinical Sample of Children. J Clin Child Adolesc Psychol 2:1-16, 2014 [Epub ahead of print].

Young RC, Biggs JT, Ziegler VE, Meyer DA: A rating scale for mania: Reliability, validity and ~~sensisivity~~sensitivity. The British Journal of Psychiatry 133: 429-435, 1978.

Youngstrom EA, Birmaher B, Findling RL: Pediatric bipolar disorder: Validity, phenomenology, and recommendations for diagnosis. Bipolar Disorders 10(1):194-214, 2008.

Youngstrom EA, Fraizer TW, Demeter C, Calabrese JR, Findling RL: Developing a ten item mania scale from the Parent General Behavior Inventory for children and adults. J Clin Psychiatry 69(5):831-839, 2008.

Youngstrom EA, Choukas-Bradley S, Calhoun CD, Jensen-Doss A: Clinical guide to the evidence-based assessment approach to diagnosis and treatment. Cognitive and Behavioral Practice: 22(1):20-35, 2014.

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

Formatted: Line spacing: Double

For Peer Review Only/Not for Publication

For Peer Review Only/Not for Distribution

Running Head: DMDD & BP-NOS: Similarities and Differences

Disruptive Mood Dysregulation Disorder and Bipolar Disorder Non-Specified: Fraternal or Identical Twins?

Mary A. Fristad, Ph.D. [a]

Hannah Wolfson, B.A. [a]

Guillermo Perez Algorta, Ph.D. [b]

Eric A. Youngstrom, Ph.D. [c]

L. Eugene Arnold, M.D., M. Ed. [a]

Boris Birmaher, M.D. [d]

Sarah Horwitz, Ph.D. [e]

David Axelson, M.D. [a, f]

Robert A. Kowatch, M.D., Ph.D. [a, f]

Robert L. Findling, M.D., M.B.A. [g]

a. Department of Psychiatry and Behavioral Health, The Ohio State University Wexner Medical Center, Columbus, OH
b. Division of Health Research, Lancaster University, Lancaster UK
c. Department of Psychology, University of North Carolina, Chapel Hill, NC
d. Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, PA
e. Department of Child and Adolescent Psychiatry, New York University School of Medicine, New York, NY
f. Section of Child and Adolescent Psychiatry, Nationwide Children's Hospital, Columbus, OH
g. Department of Psychiatry, Johns Hopkins Children's Center/ Kennedy Krieger Institute, Baltimore, MD

And the LAMS Group (Drs. Frazier, Holland, Phillips, Taylor)

Mailing Address: Mary A. Fristad, Ph.D.
Department of Psychiatry and Behavioral Health
The Ohio State University
1670 Upham Drive Suite 460G
Columbus, OH 43210-1250
Email: mary.fristad@osumc.edu
614-293-4572 office, 614-293-4949 fax

Support for this manuscript was provided by the National Institute of Mental Health: R01 MH073801, R01-MH073967, R01-MH073953, R01-MH073816.

For Peer Review Only/Not for Distribution

For Peer Review Only/Not for Distribution

Abstract

Objective: To examine similarities and differences between disruptive mood dysregulation disorder (DMDD) and bipolar disorder-not otherwise specified (BP-NOS) in baseline socio-demographic and clinical characteristics and 36-month course of irritability in children aged 6-12.9. **Methods:** 140 children with DMDD and 77 children with BP-NOS from the Longitudinal Assessment of Manic Symptoms cohort were assessed at baseline, then reassessed every six months for 36 months. **Results:** Groups were similar on most socio-demographic and baseline clinical variables other than unfiltered (i.e., interviewer-rated regardless of occurrence during a mood episode) Young Mania Rating Scale (YMRS) items. Children with DMDD received lower scores on every item (including irritability) except impaired insight; differences were significant except sexual interest and disruptive-aggressive behavior. Youth with DMDD were significantly less likely to have a biological parent with a bipolar diagnosis compared to youth with BP-NOS. Children with DMDD were more likely to be male and older than children with BP-NOS, both small effect sizes, but had nearly double the rate of disruptive behavior disorders (large effect). Caregiver ratings of irritability based on the Child and Adolescent Symptom Inventory-4R (CASI-4R) were comparable at baseline, the DMDD group had a small but significantly steeper decline in scores over 36 months relative to the BP-NOS group (b =-.24, se = .12, *95% CI* -.48 to -.0004). Trajectories for both groups were fairly stable, in the mid-range of possible scores. **Conclusion:** In a sample selected for elevated symptoms of mania, twice as many children were diagnosed with DMDD than BP-NOS. Children with DMDD and BP-NOS are similar on most characteristics other than manic symptoms, per se, and parental history of bipolar disorder. Chronic irritability is common in both groups. Comprehensive evaluations are needed to

diagnose appropriately. Clinicians should not assume that chronic irritability leads exclusively to a DMDD diagnosis.

Keywords: DMDD, BP-NOS, longitudinal, phenomenology

For Peer Review Only/Not for Distribution

For Peer Review Only/Not for Distribution

Disruptive Mood Dysregulation Disorder and Bipolar Disorder Not Otherwise Specified: Fraternal or Identical Twins?

Disruptive mood dysregulation disorder (DMDD) was added to the *DSM-5* in large part to decrease the over-diagnosis of bipolar spectrum disorders (BPSD), including bipolar disorder not-otherwise-specified (BP-NOS; in DSM-5, this diagnosis is incorporated into Other Specified Bipolar and Related Disorders, or OSBARD) (American Psychiatric Association 2013). Although temper outbursts and irritability are common symptoms in youth presenting to outpatient clinics, by definition, DMDD is characterized by persistent, non-episodic irritability and/or anger that go far beyond the severity and frequency of typical temper tantrums, with symptoms occurring persistently over at least one year (American Psychiatric Association 2013). Additionally, by definition, youth with DMDD maintain an irritable and/or angry mood between outbursts, whereas youth with BP-NOS may return to a euthymic state and are more likely to show spontaneous fluctuations or episodes (Findling, Kowatch, & Post, 2003)(Leibenluft, 2011; E A Youngstrom, Birmaher, & Findling, 2008).

Previous studies examined a precursor to DMDD called severe mood dysregulation (SMD; Leibenluft, 2011). Towbin and colleagues (2013) summarized the similarities and differences between SMD and BP-NOS based on their respective definitions. Chronic irritability is required for SMD and allowable, but not required for BP-NOS. A history of distinct, recurrent manic or hypomanic episodes that are too brief in duration (typically two to three days) to meet criteria for bipolar disorder type I or II are exclusionary for SMD but required for BP-NOS. A family history of bipolar disorder and the likelihood of converting to bipolar disorder type I or II

within seven years is unlikely for SMD but is true for approximately half of those with BP-NOS. A history of a full duration manic episode is exclusionary for both SMD and BP-NOS, as is a history of hypomania. (For the BP-NOS group, this is only true if there is also a history of MDD, which would lead to a diagnosis of bipolar disorder type II.) However, empirical comparison of these two diagnoses is quite limited.

The majority of research conducted on SMD has used data collected from a highly selected sample from the National Institute of Mental Health (NIMH) Intramural Program. Within a sample of 146 youth who met the SMD phenotype, the majority were male (66%) and had elevated rates of ADHD (86%), oppositional defiant disorder (ODD) (85%) and anxiety disorders (58%) (Leibenluft 2011). Although SMD includes the main criteria of DMDD, it also requires symptoms of hyperarousal similar to those of attention-deficit/hyperactivity disorder (ADHD) (Leibenluft et al. 2003). While some research suggests similarities between SMD/DMDD and bipolar disorder, such as deficits in facial emotion labeling (Guyer et al. 2007), differences are more common. In an epidemiologic examination of parental psychiatric history, parents of youth with SMD were significantly less likely to be diagnosed with a BPSD than parents of youth with a BPSD (2.7% versus 33.3%) (Brotman et al. 2007). Stringaris and colleagues (2010) examined the longitudinal course of this cohort and reported the children with SMD were 50 times less likely to develop a (hypo-)manic or mixed episode compared to youth with bipolar disorder.

According to a community-based follow-up study, SMD has a lifetime prevalence of 3.3% in youth aged 9 to 19; at an eight-year follow-up, youth diagnosed with SMD at an average age of 10 were significantly more likely than those not diagnosed with SMD to have a depressive disorder by age 18 (odds ratio 7.2, confidence interval 1.3-38.8, $p = .02$) but not bipolar disorder

For Peer Review Only/Not for Distribution

(Brotman et al. 2006). Of note, of those participants without SMD, a quarter had other diagnoses, including any emotional disorder, 6.1%, any behavioral disorder, 19.6%, any anxiety disorder, 4.5% or substance abuse/dependence, 8.8% (Brotman et al. 2006). Copeland and colleagues (2014) followed this cohort into adulthood. Those with SMD (using retrofitted criteria to meet DMDD criteria by these authors) were significantly more likely than those without SMD/DMDD to have an adult depressive or anxiety disorder and they had a 10.3 greater odds of having multiple adult disorders than those without SMD/DMDD (Copeland et al. 2014). The authors did not report on presence/absence of bipolar disorder, so it is unknown if rates differed in adulthood between participants who did versus did not meet criteria for SMD/DMDD as children.

A small number of studies have characterized DMDD. Within a large community sample of 6-year-old children, 8% met criteria for DMDD when criteria were retrospectively applied. Of these, 61% demonstrated comorbidity with an emotional or behavioral disorder (Dougherty et al. 2014). Participants with DMDD had significantly higher rates of oppositional defiant disorder and depression than participants without DMDD (55% vs 5%, 13% vs 5%, respectively) (Dougherty et al. 2014). Both ODD and ADHD at 3 years of age predicted DMDD at age 6 (Dougherty et al. 2014). Familial and environmental predictors included low parental support, lower levels of marital satisfaction, and parental lifetime substance use disorders. However, parental internalizing disorders were not associated with a DMDD diagnosis at age 6 (Dougherty et al. 2014).

Axelson et al. (2012) utilized the Longitudinal Assessment of Manic Symptoms (LAMS) sample to characterize children who met all DSM-5 DMDD criteria, with the exception being that participants with BPSD were allowed in the DMDD group. Just over one-fourth (26%) of the LAMS sample met DMDD criteria at baseline. Results indicated significantly higher rates of

For Peer Review Only/Not for Distribution

ADHD (79%), disruptive behavior disorders (96%; ODD, 78%; conduct disorder, 18%) in children who met DMDD compared to those who did not meet criteria for DMDD. In addition, youth with DMDD had significantly elevated scores on dimensional measures of mania and depression, and were more impaired than those without DMDD.

Sparks and colleagues (2014) examined offspring of parents who had bipolar disorder. They reported that these offspring were more likely than offspring of community control parents to meet DMDD criteria (odds ratio 8.3, 6.7% versus 0.8%) and to have higher rates of chronic irritability (12.5% versus 2.5%, $p < .005$). Chronic irritability was noted in offspring who had diagnoses of bipolar disorder, depression, ADHD and disruptive behavior disorders.

Margulies and colleagues (2014) examined rates of DMDD in 82 consecutive psychiatrically hospitalized children. They reported that nearly one-third (31%) of children met DMDD criteria by parental report; however, only half of these (16%) did when diagnosis was based on inpatient observation. Over half (56%) of the 82 children had parent-reported manic symptoms (scores ≥20 on the Child Mania Rating Scale-Parent form). Of these 46, nearly half (n=21; 46%) met DMDD by parental report but only one-third (17.4%) did based on inpatient observation. The authors conclude "The overall utility of the DMDD diagnosis and whether it would prevent children from receiving other and better-defined diagnoses remains to be seen." (p. 495).

To date, no one has compared DMDD directly to BP-NOS to determine the similarities and differences between these two diagnoses over time. Cross-sectionally, of course, the two diagnoses are expected to exhibit similarities (and therefore, the new diagnosis of DMDD is intended to decrease the misdiagnosis of bipolar disorder), but their longitudinal courses are expected to differ. This is important as treatment, particularly pharmacologic interventions, likely

For Peer Review Only/Not for Distribution

will differ for these two diagnoses. If DMDD develops into depressive and/or anxiety disorders, anti-depressant treatment would be a logical first pharmacologic treatment of choice. Alternately, if DMDD continues to show a more externalizing behavior trajectory--consistent with the overlap in symptoms with oppositional-defiant disorder (Axelson et al. 2011) and the cross-sectional comorbidities with disruptive behavior disorders noted above – then a different treatment package of psychosocial (Eyberg, Nelson, & Boggs, 2008) and pharmacological interventions would be indicated (Jensen et al. 2007). In contrast, if BP-NOS continues to express itself as part of the bipolar continuum, atypical antipsychotics and/or mood stabilizers likely would be the first pharmacologic treatment of choice (McClellan, Kowatch, & Findling, 2007). Thus, it is crucial to develop clear templates for clinicians so they can precisely differentiate youth with DMDD from youth with BP-NOS.

This study used a longitudinal cohort to compare children who met diagnostic criteria for DMDD or BP-NOS at entry into the study. First, we determined whether the two groups differed on a variety of socio-demographic and clinical variables. Second, we evaluated group differences in participants' parent-rated irritability over a 36 month follow-up period. We hypothesized that youth with DMDD and BP-NOS would have many similarities on symptoms common in outpatient clinics (e.g., irritability, aggression, impulsivity) but that children with DMDD versus BP-NOS would differ, by definition, in their expression of classically manic symptoms (e.g., euphoric mood, decreased sleep). Further, given the diagnostic criteria for DMDD, the two groups should exhibit distinct irritability trajectories, with DMDD participants maintaining consistently higher levels of irritability than youth with BP-NOS, whose irritability should be largely confined to episodes.

Method

For Peer Review Only/Not for Distribution

Ascertainment of this sample has been described in detail elsewhere (Horwitz et al, 2010; Findling et al, 2010). In summary, institutional review boards at each university-affiliated LAMS sites (Case Western Reserve University, Cincinnati Children's Medical Center, the Ohio State University, and the University of Pittsburgh Medical Center) approved all procedures. Parents/guardians at outpatient clinics provided written informed consent before completing the screening procedure, which consisted of a brief demographic form and the PGBI-10M (Youngstrom et al. 2008) to screen for elevated symptoms of mania (ESM). Results from this screening were used to invite a group of ESM+ children and a smaller, demographically matched sample of ESM- children to enroll into the longitudinal portion of the study, for which parents provided consent and the children, assent prior to their participation.

Sample

A subsample of 217 children aged 6 to 12.9 years from the LAMS cohort (N=685) were included in the current study on the basis of a BP-NOS (n=77) or DMDD (n=140) diagnosis (defined below) at baseline. In youth from the original cohort, the diagnoses most commonly assigned at baseline were: ADHD (76.1%), other disruptive behavior disorders (51.1%), bipolar spectrum disorders (22.9%), depressive disorders (17.5%) and anxiety disorders (31.3%) (Findling et al. 2010).

Measures

Demographics. Parents/guardians provided information including age, sex, race, ethnicity, and health insurance status.

Family History. The Family History Screen (Weissman et al. 2000) was completed to collect information on parental psychiatric disorders. In addition to presence or absence of manic symptoms, parents were considered to have a probable bipolar disorder if they had elated mood

For Peer Review Only/Not for Distribution

plus three additional symptoms of mania or irritable mood plus four additional symptoms of mania.

Psychiatric Diagnoses. Trained interviewers administered to children and their parent or legal guardian the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL), with additional items about depressive and manic symptoms from the Washington University St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL-W) (Kaufman et al. 1997; Geller et al. 2001). Additional questions were added to screen for pervasive developmental disorders. Study interviewers completed this semi-structured interview to assess current and lifetime psychiatric diagnoses and the duration of each illness. Mood disorder diagnoses were evaluated at the baseline assessment and every six months afterwards.

DMDD Diagnosis. DMDD in the LAMS sample was originally operationalized by Axelson et al. (2012) using K-SADS-PL-W items. For this study, we excluded 44 participants with bipolar diagnoses (n=27 who met criteria for DMDD and BP-NOS, these participants were included in the BP-NOS group; n=16, bipolar type 1; n=1, cyclothymic disorder) from the DMDD group to more closely resemble *DSM*-5 criteria (American Psychiatric Association 2013).

- **Severe recurrent temper outbursts.** This criterion was derived from the "loses temper" item (at threshold, frequency is 2-5 times per week).
- **Chronic irritability.** This criterion was derived from the oppositional defiant disorder section of the behavioral disorders supplement: "easily annoyed or angered" and "angry or resentful" items (both at threshold).

For Peer Review Only/Not for Distribution

- **Duration.** Participants administered the K-SADS-PL-W oppositional defiant disorder supplement were assessed for the presence of symptoms for a least 6 months, regardless of if they met full criteria for oppositional defiant disorder. DMDD criterion states that symptoms must have been present for at least 12 months, with no more than 3 consecutive months when the person was without the preceding diagnostic criteria.
- **Impairment in more than 1 setting.** The oppositional defiant disorder section of the behavioral disorders supplement evaluated impairment in at least 2 settings.
- **No presence of a BPSD diagnosis**. Youth with any bipolar spectrum disorder (i.e., bipolar I or II disorder, BP-NOS, cyclothymia) were excluded.

BP-NOS Diagnosis. The LAMS study uses previously developed criteria from the Course and Outcomes of Bipolar Youth (COBY) study to diagnose BP-NOS (Birmaher et al, 2009). These are:

- Child does not meet the DSM-IV criteria for bipolar disorder type I or II
- A distinct period of abnormally elevated, expansive, or irritable mood plus the following

  1. 2 DSM-IV-TR B-criterion manic symptoms (3 if the mood is irritability only) that are clearly associated with onset of abnormal mood

  2. A clear change in functioning

  3. Presence of elated and/or irritable mood and manic symptoms for a significant part of the day (4 h, although this does not necessarily need to be expressed consecutively)

For Peer Review Only/Not for Distribution

4. 4 days (not necessarily consecutive) meeting criteria B.1eB.3 over patient's lifetime

C. Mood and affective symptoms must be abnormal for child's level of development and environment

- Symptoms or mood changes that occur during substance use or antidepressant treatment do not count toward a bipolar diagnosis
- Exclusion criteria

  1. Current or lifetime DSM-IV diagnosis of schizophrenia, mental retardation, autism, or severe autism spectrum disorders

  2. Mood disorders due to substance abuse, a medical condition, or secondary to use of medications (e.g., corticosteroids)
- If onset occurs prior to onset of comorbid substance use disorders, cases are included
- Children with mild comorbid Asperger disorder or pervasive developmental disorder not otherwise specified are included if their mood symptomatology was clearly episodic and best accounted for by the bipolar diagnosis

Medication History. Parents/guardians provided a comprehensive history of the child's past and current psychotropic medication usage.

Functional Assessment. Study interviewers assigned ratings on the Children's Global Assessment Scale (CGAS) following completion of their comprehensive evaluation to assess the severity of current and lifetime impairment (Shaffer et al. 1983). The CGAS captures children's functionality at home, at school, and with peers.

For Peer Review Only/Not for Distribution

Mood Ratings. Unfiltered (meaning that severity of the symptom was rated regardless of whether it occurred in the context of a mood episode) (Yee et al. 2014) ratings of manic and depressive symptoms that occurred in the past 2 weeks were obtained via interview of the child and parent/guardian using the Young Mania Rating Scale (YMRS) and the Children's Depression Rating Scale- Revised (CDRS-R) (Young et al. 1978; Poznanski et al. 1984). In contrast to methodology used by Axelson et al. (2012), the current study included total scores of irritability items so that scores from the two diagnostic groups in this study could be compared to results from other studies.

Questionnaires. Several self-report measures were completed by caregivers to characterize children's symptoms. Elevated symptoms of mania were assessed using the PGBI-10M (Youngstrom et al. 2008). Anxiety symptoms during the past 6 months were obtained from the Screen for Child Anxiety Related Emotional Disorders (SCARED-P) (Birmaher et al. 1997).

Irritability Scale. An irritability scale was derived from items found in the Child and Adolescent Symptom Inventory-4R (CASI-4R) ADHD, oppositional defiant disorder, and conduct disorder subscales (Gadow and Sprafkin 2005). This was done to generate a continuous irritability variable based on caregiver report of the child's symptoms. To secure content validity with a previous well-validated irritability scale, Affective Reactivity Index items (Stringaris et al. 2012), were considered in the selection of CASI-4R items. Six items were identified from the CASI-4R that mapped onto the ARI items: 1) loses temper; 2) irritable for most of the day; 3) touchy or easily annoyed; 4) angry or resentful; 5) extremely tense or unable to relax; 6) deliberately annoys others. Principal axis factor analysis confirmed a single factor solution that showed an excellent level of reliability (Cronbach's alpha = 0.87).

Analyses

For Peer Review Only/Not for Distribution

Statistical analyses used IBM SPSS version 22.0 (IBM Corp. 2013) and R (R Core Team 2014). Unweighted means, standard deviations, and frequency counts were calculated for descriptive statistics. Between-group differences were assessed with chi square analyses for binary variables and independent t-tests for continuous variables. Cohen's *d* effect size using the pooled standard deviation and *phi*'s for chi-squares were computed.

To compare caregiver-reported irritability level at baseline and during the 36-month follow-up observation between diagnostic groups, a hierarchical linear model, with a random intercept and slope, with repeated measures nested within subject (level 1), and time and diagnostic group as fixed covariates (level 2), was used. The diagnostic group*time interaction was the key outcome, with the coding using DMDD as the target and BP-NOS as the comparison. A model-based (semi) parametric bootstrap method was used to generate 95% confidence intervals based on 10000 bootstrap replicates.

Results

Baseline Comparisons

First, demographic variables were compared between the 140 children who met criteria for DMDD and the 77 who met criteria for BP-NOS. Significant age and sex differences between diagnostic groups were observed (Table 1). Children with DMDD were more likely to be male and younger than children with BP-NOS, with small effect sizes for both factors. There were no significant differences between groups in clinical treatment history. When baseline clinical characteristics were compared, children with DMDD had lower levels of manic symptoms but nearly double the rate of disruptive behavior disorders, with large effect sizes for both factors.

When specific items on the unfiltered (i.e., rated regardless of occurrence within a mood episode) interviewer-rated YMRS were compared, children with DMDD averaged equal or lower

For Peer Review Only/Not for Distribution

scores on every item except impaired insight; all differences were significant except for sexual interest and disruptive-aggressive behavior (Table 2). Of note, children with DMDD had lower YMRS irritability scores than children with BP-NOS. Participants with DMDD did not significantly differ from those with BP-NOS in presence or absence of any manic symptoms in biological parents. However, participants with DMDD were significantly less likely than those with BP-NOS to have a biological parent with a probable bipolar spectrum diagnosis (19% vs 31%, p<.05).

Longitudinal Comparison

The distribution of scores on the Irritability Scale, which is based on caregiver-report of the child's behavior, was approximately normal for the two groups combined, with no outliers (Figure 1). At baseline, although caregivers of children with DMDD rated them higher on irritability than caregivers of children with BP-NOS, this did not reach statistical significance (*b* =.51, *se* = .48, *t-test* = 1.07, *p*>.05, Table 3). Irritability decreased slightly faster for the DMDD group over the 36 month-follow up period (*b* =-.24, *se* = .12, *t-test* = -1.96, *p*=.0499). Trajectories for both groups were fairly stable, in the mid-range of possible scores (Figure 2).

As there were 27 children who fulfilled criteria for DMDD (other than the bipolar symptom exclusion) and BP-NOS, we completed one additional post-hoc comparison, comparing rates of irritability between three groups, DMDD+BP-NOS (n=27), DMDD only (n=140) and BP-NOS only (n=50). The DMDD+BP-NOS and DMDD groups had higher levels of caregiver-reported irritability at baseline than the BP-NOS only group. The only significant difference in slopes was between DMDD only and DMDD+BP-NOS, with the latter group showing the slowest decline in irritability (b=0.38, 95% [.02 - .74].

Discussion

For Peer Review Only/Not for Distribution

We evaluated similarities and differences between DMDD and BP-NOS on socio-demographic and clinical variables at baseline, particularly YMRS items, and tested whether rates of caregiver-reported irritability differed between the two groups over time. DMDD was not clearly distinguished from BP-NOS on most comparison points other than YMRS items and rates of a probable bipolar diagnosis in biological parents. Of note, the YMRS was administered in an unfiltered manner (i.e., in a "what you see is what you get" manner regardless of whether the symptoms occurred within the context of a mood episode) and was not used to make the diagnosis of DMDD or BP-NOS (for a further discussion of this, see Yee et al. 2014).

Children with DMDD were younger and more likely to be boys. However, these were not striking differences—average ages for both groups were in the 9 to 10 year old range and boys were the majority of each group. Youth with DMDD were similar to those with BP-NOS on most clinical factors including: number of diagnoses; number of medications; likelihood of prior hospitalization; comorbid ADHD, anxiety disorders, pervasive developmental disorders, elimination disorders, and psychosis; global impairment; PGBI-10M; and depressive and anxiety symptom severity. Only disruptive behavior disorders were more common in children with DMDD, consistent with prior research (Stringaris et al. 2010; Axelson et al. 2012; Towbin et al. 2013). Irritability on the parent-reported Irritability Scale was nominally higher at baseline, but to a non-significant degree, for the DMDD group, compared to the BP-NOS group, but then decreased more rapidly over time. The difference in slopes was statistically significant, but unlikely to be clinically meaningful. The change of a quarter point is miniscule, given that the scale is only accurate to +/-1.90 points for individual change scores, based on the standard error of the difference score (Jacobson & Truax, 1991).

For Peer Review Only/Not for Distribution

YMRS total scores and all item scores except impaired insight (which was negligibly different between groups) were similar or lower for children with DMDD compared to children with BP-NOS. Notably, elevated mood, increased motor activity, decreased sleep, pressured speech, impaired language/thought, thought content, and appearance were all more elevated in children with BP-NOS. Even irritability on the YMRS was more severe for children with BP-NOS.

Group comparisons of caregiver-reported irritability revealed three findings of interest. First, the groups did not differ significantly on either the level or change over time in ratings of irritability. While there was a small decrement in irritability scores over time for the DMDD group, irritability remained stable in the BP-NOS group. Second, both groups had mid-range irritability scores of 10-12 on a 0-18 scale that remained fairly consistent over the three years. Although the presence of both DMDD and BP-NOS is disallowed per DSM-5 rules, when the subgroup who met criteria for both diagnoses (other than the manic symptom exclusion for DMDD) was compared on chronic irritability to those children who had DMDD only or BP-NOS only, the DMDD+BP-NOS children had significantly less decline in caregiver-reported irritability over time.

Differences in findings regarding irritability, depending on whether the interviewer rated presence/absence and severity based on a "what you see is what you get" unfiltered manner or whether caregivers reported on their children's behavior, are interesting. Children with DMDD appeared less impaired than children with BP-NOS using the former strategy, but the two groups appeared similar when using caregiver report on rating scales. Perhaps the frustration of raising a child with a disruptive behavior disorder, which were ubiquitous in the DMDD group, leads to higher caregiver reports of irritability, whereas interviewer-based questioning that incorporates

For Peer Review Only/Not for Distribution

parent and child input as well as clinical observation during the interview, puts a greater perspective on the severity of the behaviors and affect observed. This is in keeping with previous research showing much lower rates of DMDD when diagnoses are based on clinical observation rather than parental self-report (Margulies et al., 2014).

DMDD was included in the DSM-5 as a way to decrease diagnoses of BPSD in children. Pharmacologic management, in particular, might differ for children with DMDD compared to those with BP-NOS. Children with DMDD initially display high rates of externalizing symptoms and comorbid disruptive behavior disorders with subsequent risk for development of depressive disorders, which would suggest treatment with antidepressant medications. Those with BP-NOS are likely to be treated with first-line medications for bipolar disorder. Clarifying the differentiating features of DMDD and BP-NOS is therefore crucial for the effective management of these disorders. Results from this study point to cross-sectional similarities between these two diagnostic groups on nearly every feature except more classically manic symptoms and family history of probable bipolar disorder in parents. Further, the trajectory of caregiver-reported irritability over a three year interval does not meaningfully separate the two groups. Thus, it will be important for clinicians not to use caregiver-reported chronic irritability in isolation as a reason to consider DMDD the most appropriate diagnosis, but rather to conduct a thorough review of symptoms and course to determine if a child fulfills DMDD, BP-NOS or other primary and co-morbid diagnoses. In this regard, it is noteworthy that clinicians achieved lower reliability for DMDD than for pediatric bipolar diagnoses in the DSM-5 field trials (Regier et al. 2012). Semi-structured approaches (Rettew, Lynch, Achenbach, Dumenci, & Ivanova, 2009) or checklists as a way of augmenting the family's description of the presenting problem could be

For Peer Review Only/Not for Distribution

helpful in improving the reproducibility of diagnoses (Croskerry, 2003; Gawande, 2010; Youngstrom, Choukas-Bradley, Calhoun, & Jensen-Doss, 2014).

Several limitations of this study are important to note. The current study utilized retrofitted K-SADS-PL-W responses to determine DMDD diagnoses. Our criteria slightly modified those previously reported in Axelson et al. (2012) to better align with *DSM*-5 diagnostic criteria. The majority of LAMS study participants were recruited due to their elevated PGBI-10M scores, resulting in a sample with disproportionately elevated symptoms of mania and therefore, not fully representative of clinical outpatient samples. Despite these limitations, these findings suggest that children with DMDD and BP-NOS are very similar on most characteristics other than manic symptoms and a probable bipolar family history. Even in a sample enriched with children who have elevated symptoms of mania, DMDD outnumbers a BP-NOS diagnosis almost 2:1. Clinicians will need to complete comprehensive evaluations to appropriately diagnose children and not assume that caregiver-reported chronic irritability leads exclusively to a DMDD diagnosis. Children with DMDD and BP-NOS are fraternal, not identical twins, but they may easily confuse the casual observer.

For Peer Review Only/Not for Distribution

For Peer Review Only/Not for Distribution

References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2013.

Axelson DA, Birmaher B, Findling RL, Fristad MA, Kowatch RA, Youngstrom EA, Arnold EL, Goldstein BI, Goldstein TR, Chang KD, Delbello MP, Ryan ND, Diler RS: Concerns regarding the inclusion of temper dysregulation disorder with dysphoria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. J Clin Psychiatry 72(9):1257-1262, 2011.

Axelson D, Findling R, Fristad MA, Kowatch RA, Youngstrom EA, Horwitz SM, Arnold E, Frazier TW, Ryan N, Demeter C, Gill MK, Hauser-Harrington JC, Depew J, Kennedy SM, Gron BA, Rowles BM, Birmaher B: Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the Longitudinal Assessment of Manic Symptoms study. J Clin Psychiatry 73(10):1342-1350, 2012.

Birmaher B, Khetarpal S, Brent D, Cully M, Balach L, Kaufman J, Neer SM: The Screen for Child Anxiety Related Emotional Disorders (SCARED): Scale construction and psychometric characteristics. J Am Acad Child Adolesc Psychiatry 36(4):545-553, 1997.

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 C, Goldstein T, Ryan N, Keller M: Four-year longitudinal course of children and adolescents with bipolar spectrum disorder: The course and outcome of bipolar youth (COBY) study. Am J Psychiatry 166(7):795-804, 2009.

Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, Egger HL, Angold A, Pine DS, Leibenluft E: Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biol Psychiatry 60:991-997, 2006.

Brotman MA, Kassem L, Reising MM, Guyer AE, Dickstein DP, Rich BA, Towbin KE, Pine DS, McMahon FJ, Leibenluft E: Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation. Am J Psychiatry, 164(8):1238-1241, 2007.

Copeland WE, Shanahan L, Egger H, Angold A, Costello EJ: Adult diagnostic and functional outcomes of DSM-5 disruptive mood dysregulation disorder. Am J Psychiatry, 171:668-674, 2014.

Croskerry P: The importance of cognitive errors in diagnosis and strategies to minimize them. Academic Medicine, 78(8):775-780, 2003.

Deveney CM, Hommer RE, Reeves E, Stringaris A, Hinton KE, Haring CT, Vidal-Ribas P, Towbin K, Brotman M, Leibenluft E: A prospective study of severe irritability in youths: 2- and 4-year follow-up. Depression and Anxiety, 00:1-9, 2014.

Dougherty LR, Smith VC, Bufferd SJ, Carlson GA, Stringaris A, Leibenluft E, Klein DN: DSM-5 disruptive mood dysregulation disorder: Correlates and predictors in young children. Psychological Medicine, 44:2339-2350, 2014.

Eyberg SM, Nelson MM & Boggs SR: Evidence-based psychological treatments for children and adolescents with disruptive behavior. Journal of Clinical Child and Adolescent Psychology, 37(1):215-237, 2008.

Findling RL, Kowatch RA, & Post RM: Pediatric bipolar disorder: A handbook for clinicians. London: Martin Dunitz, 2003.

Findling RL, Youngstrom EA, Fristad MA, Birmaher B, Kowatch RA, Arnold LE, Frazier TW, Axelson D, Ryan N, Demeter CA, Fields B, Depew J, Kennedy SM, Marsh L, Rowles BM, Horwitz SM: Characteristics of children with elevated symptoms of mania: the

For Peer Review Only/Not for Distribution

Longitudinal Assessment of Manic Symptoms (LAMS) study. J Clinc Psychiatry, 71(12): 1664-1672, 2010.

Gadow KD, Sprafkin J: Child and Adolescent Symptom Inventory-4R. Checkmate Plus: Stony Brook, NY: 2005.

Gawande, A. The Checklist Manifesto. New York, NY: Penguin. (2010).

Geller B, Zimerman B, Williams M, Bolhofner K, Craney J, DelBello MP, Soutullo C: Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. J Am Acad Child Adolesc Psychiatry 40(4):450-455, 2001.

Guyer AE, McClure EB, Adler AD, Brotman MA, Rich BA, Kime AS, Pine DS, Ermst M, Leibenluft E: Specificity of facial expression labeling deficits in childhood psychopathology. Journal of Child Psychology and Psychiatry, 48(9):863-871, 2007.

Horwitz SM, Demeter CA, Pagano ME, Youngstrom EA, Fristad MA, Arnold LE, Birmaher B, Gill MK, Axelson D, Kowatch RA, Frazier TW, Findling RL: Longitudinal Assessment of Manic Symptoms (LAMS) study: Background, design, and initial screening results. The Journal of Clinical Psychiatry 71(11): 1511-1517, 2010.

IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol, 59, 12-19.

Jensen PS, Youngstrom EA, Steiner H, Findling RL, Meyer RE, Malone RP, Carlson GA, Coccaro EF, Aman MG, Blair J, Dougherty D, Ferris C, Flynn L, Green E, Hoagwood K, Hutchinson J, Laughren T, Leve LD, Novins DK, Vitello B: Consensus report on impulsive

For Peer Review Only/Not for Distribution

aggression as a symptom across diagnostic categories in child psychiatry: Implications for medication studies. J Am Acad Child Adolesc Psychiatry 46(3):309-322, 2007.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N: 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 36(7): 980-988, 1997.

Leibenluft E, Dennis CS, Towbin KE, Bhangoo RK, Pine DS: Defining clinical phenotypes of juvenile mania. Am J Psychiatry 160(3):430-437, 2003.

Leibenluft E: Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatry 168(2):129-142, 2011.

Margulies DM, Weintraub S, Basile J, Grover PJ, Carlson GA: Will disruptive mood dysregulation disorder reduce false diagnosis of bipolar disorder in children? Bipolar Disorders 14:488-496, 2012.

McClellan J, Kowatch R, & Findling RL: Practice Parameter for the assessment and treatment of children and adolescents with bipolar disorder. Journal of Child & Adolescent Psychiatry 46(1):107-125, 2007.

Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, Gibbons R: Preliminary studies of the reliability and validity of the Children's Depression Rating Scale. Journal of the American Academy of Child Psychiatry 23(2):191-197, 1984.

R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

For Peer Review Only/Not for Distribution

Rettew DC, Lynch AD, Achenbach TM, Dumenci L, Ivanova MY: Meta-analyses of agreement between diagnoses made from clinical evaluations and standardized diagnostic interviews. International Journal of Methods in Psychiatric Research 18(3):169-184, 2009.

Roy AK, Lopes V, Klein RG: Disruptive Mood Dysregulation Disorder: A new diagnostic approach to chronic irritability in youth. Am J Psychiatry 171:918-924, 2014.

Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S: A Children's Global Assessment Scale (CGAS). Arch Gen Psychiatry 40:1228-1231, 1983.

Sparks GM, Axelson DA, Haifeng Y, Ha W, Ballester J, Diler RS, Goldstein B, Goldstein T, Hickey MB, Ladouceur CD, Monk K, Sakolsky D, Birmaher B: Disruptive mood dysregulation disorder and chronic irritability in youth at familial risk for bipolar disorder. Journal of the American Academy of Child & Adolescent Psychiatry: 53(4):408-416, 2014.

Stringaris A, Cohen P, Pine D, Leibenluft E: Adult outcomes of youth irritability: A 20-year prospective community-based study. Am J Psychiatry 166(9):1048-1054, 2009.

Stringaris A, Baroni A, Haimm C, Brotman M, Lowe CH, Myers F, Rustgi E, Wheeler W, Kayser R, Towbin K, Leibenluft E: Pediatric bipolar disorder versus severe mood dysregulation: Risk for manic episodes on follow-up. Journal of the American Academy of Child and Adolescent Psychiatry 49(4):397-405, 2010.

Stringaris A, Goodman R, Ferdinando S, Razdan V, Muhrer E, Leibenluft E, Brotman M: The Affective Reactivity Index: A concise irritability scale for clinical and research settings. Journal of Child Psychology and Psychiatry 53(11):1109-1117, 2012.

Towbin K, Axelson D, Leibenluft E, Birmaher B: Differentiating bipolar disorder-not otherwise specified and severe mood dysregulation. Journal of the American Academy of Child & Psychiatry 52(5): 466-481, 2013.

For Peer Review Only/Not for Distribution

Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M: Brief screening for family psychiatric history: The family history screen. Arch Gen Psychiatry 57(7): 675-682, 2000.

Yee AM, Algorta GP, Youngstrom EA, Findling RL, Birmaher B, Fristad MA, The Lams Group: Unfiltered Administration of the YMRS and CDRS-R in a Clinical Sample of Children. J Clin Child Adolesc Psychol 2:1-16, 2014 [Epub ahead of print].

Young RC, Biggs JT, Ziegler VE, Meyer DA: A rating scale for mania: Reliability, validity and sensitivity. The British Journal of Psychiatry 133: 429-435, 1978.

Youngstrom EA, Birmaher B, Findling RL: Pediatric bipolar disorder: Validity, phenomenology, and recommendations for diagnosis. Bipolar Disorders 10(1):194-214, 2008.

Youngstrom EA, Fraizer TW, Demeter C, Calabrese JR, Findling RL: Developing a ten item mania scale from the Parent General Behavior Inventory for children and adults. J Clin Psychiatry 69(5):831-839, 2008.

Youngstrom EA, Choukas-Bradley S, Calhoun CD, Jensen-Doss A: Clinical guide to the evidence-based assessment approach to diagnosis and treatment. Cognitive and Behavioral Practice: 22(1):20-35, 2014.

For Peer Review Only/Not for Distribution

For Peer Review Only/Not for Distribution

Table 1

Baseline socio-demographic and clinical characteristics of children with DMDD and BP-NOS

Variable	DMDD (n=140)	BP-NOS (n=77)	*t-test* or *Chi-Square*	*Cohen's d or phi*
Age, *M±SD*	9.11±1.83	9.87±2.07	2.79**	.39
Gender, male *n (%)*	97 (69)	42 (55)	4.69*	.15
Race, white *n (%)*	82 (59)	45 (58)	0.00	
Medicaid, yes *n (%)*	80 (57)	39 (51)	0.85	
N of Meds at Baseline, *M±SD*	0.95±.98	1.04±1.16	0.60	
N of Diagnoses at Baseline, *M±SD*	2.91±1.19	3.04±1.26	0.77	
Hospitalization, yes *n (%)*	10 (7)	5 (7)	0.03	
ESM+ *n (%)*	127 (91)	75 (97)	2.94	
CGAS, *M±SD*	51.33±8.99	51.57±8.58	0.19	
YMRS, *M±SD*	17.31±7.62	25.09±7.71	7.16 ***	1.01
CDRS, *M±SD*	36.64±9.56	39.27 ±10.60	1.87	
PGBI-10M, *M±SD*	14.01±6.68	15.39±6.06	1.5	
SCARED-P, *M±SD*	17.32±12.90	17.44±10.78	0.07	
Irritability Scale, *M±SD*	11.62±3.78	12.39±3.60	-1.46	
ADHD, yes *n (%)*	118 (84)	59 (77)	1.94	
Disruptive disorder, yes *n (%)*	137 (98)	41 (53)	67.06***	.56
Anxiety, yes *n (%)*	42 (30)	26 (34)	0.33	
Elimination, yes *n (%)*	31 (22)	17 (22)	0.00	
PDD, yes *n (%)*	4 (3)	0 (0)	2.24	
Psychosis , yes *n (%)*	3 (2)	2 (3)	0.05	
Maternal history of manic symptoms, yes *n (%)*	14 (48)	15 (52)	3.86	

Paternal history of manic symptoms, yes *n (%)*	12 (9)	9 (12)	.52	
Probable diagnosis of either parent bipolar spectrum, yes *n*	26 (19)	24 (31)	4.45*	.14

Note: *p<.05, **p<.01, ***p<.001.

For Peer Review Only/Not for Distribution

For Peer Review Only/Not for Distribution

Table 2

Differences in Item-Level YMRS Scores at Baseline between the DMDD and BP-NOS Groups

Variable	DMDD (n=140)	BP-NOS (n=77)	*t-test*	*P* Value
Elevated Mood	0.79±0.99	2.12±1.31	8.41	<0.001
Increased Motor Activity Energy	1.46±1.46	2.51±1.42	5.12	<0.001
Sexual Interest	0.47±0.91	0.73±1.14	1.81	0.72
Sleep	0.54±0.98	1.08±1.29	3.428	0.001
Irritability	3.64±1.95	4.27±1.88	2.31	0.02
Speech (Rate & Amount)	1.88±1.97	3.58±2.11	5.94	<0.001
Language Thought Disorder	1.15±0.98	1.91±0.99	5.44	<0.001
Content	0.70±1.46	1.57±2.03	3.65	<0.001
Disruptive-Aggressive Behavior	4.13±1.85	4.30±1.87	0.65	0.52
Appearance	0.55±0.76	1.12±1.05	4.57	<0.001
Impaired Insight	2.01±1.53	1.91±1.48	-0.46	0.65

For Peer Review Only/Not for Distribution

Table 3

Differences in Irritability Level at Baseline and Over Time between the DMDD and BP-NOS Groups

Variable	*b estimate*	*se*	*t-test*	95% *CI*[$]
Intercept	11.45	.38	29.66	[10.69, 12.20]
Time	-.14	.10	-1.52	[-.34, .05]
Diagnostic Group (DMDD =1)	.51	.48	1.07	[-.42, 1.47]
Time*Diagnostic Group (DMDD =1)	-.24	.12	-1.96	[-.48, -.0004]

Note: [$] 95% Confidence Intervals based on 10,000 bootstrap replicates.

Figure 1

Baseline YMRS and Irritability Levels by Groups

INSERT FIGURE 1

Note: The correlation observed between Irritability and YMRS total score at baseline was $r = .07$, $p > .05$.

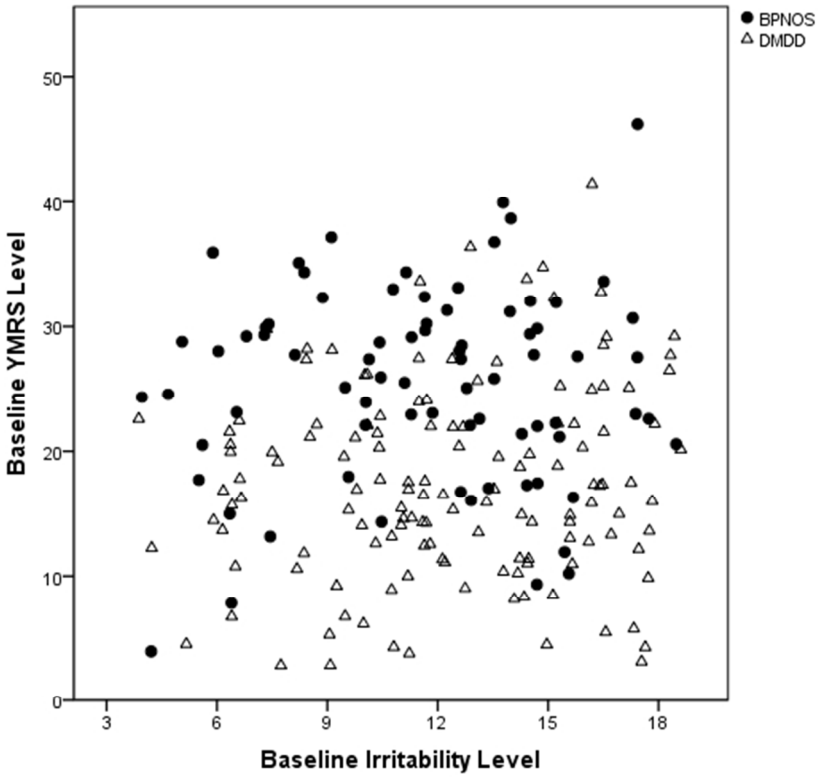
For Peer Review Only/Not for Distribution

Figure 2

Irritability Trajectories over 36-Months in Children with DMDD and BP-NOS

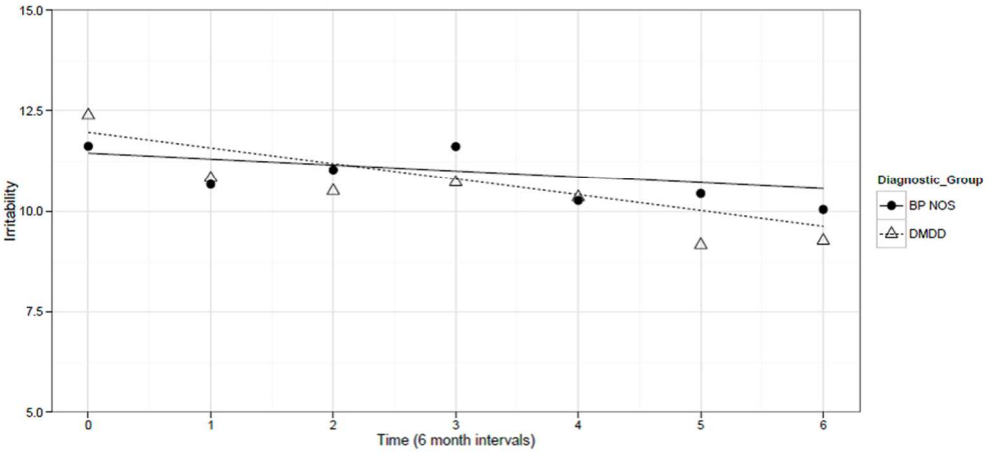
INSERT FIGURE 2

For Peer Review Only/Not for Distribution



166x133mm (96 x 96 DPI)

For Not for Distribution



237x119mm (96 x 96 DPI)

For Only/Not for Distribution

FOCUS ON CHILDHOOD AND ADOLESCENT MENTAL HEALTH

Examining the Proposed Disruptive Mood Dysregulation Disorder Diagnosis in Children in the Longitudinal Assessment of Manic Symptoms Study

David Axelson, MD; Robert L. Findling, MD, MBA; Mary A. Fristad, PhD, ABPP; Robert A. Kowatch, MD, PhD; Eric A. Youngstrom, PhD; Sarah McCue Horwitz, PhD; L. Eugene Arnold, MD; Thomas W. Frazier, PhD; Neal Ryan, MD; Christine Demeter, MA; Mary Kay Gill, MSN; Jessica C. Hauser-Harrington, PhD; Judith Depew; Shawn M. Kennedy, MA; Brittany A. Gron, BS; Brieana M. Rowles, MA; and Boris Birmaher, MD

ABSTRACT

Objective: To examine the proposed disruptive mood dysregulation disorder (DMDD) diagnosis in a child psychiatric outpatient population. Evaluation of DMDD included 4 domains: clinical phenomenology, delimitation from other diagnoses, longitudinal stability, and association with parental psychiatric disorders.

Method: Data were obtained from 706 children aged 6–12 years who participated in the Longitudinal Assessment of Manic Symptoms (LAMS) study (sample was accrued from November 2005 to November 2008). *DSM-IV* criteria were used, and assessments, which included diagnostic, symptomatic, and functional measures, were performed at intake and at 12 and 24 months of follow-up. For the current post hoc analyses, a retrospective diagnosis of DMDD was constructed using items from the K-SADS-PL-W, a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, which resulted in criteria closely matching the proposed *DSM-5* criteria for DMDD.

Results: At intake, 26% of participants met the operational DMDD criteria. DMDD+ vs DMDD– participants had higher rates of oppositional defiant disorder (relative risk [RR] = 3.9, $P < .0001$) and conduct disorder (RR = 4.5, $P < .0001$). On multivariate analysis, DMDD+ participants had higher rates of and more severe symptoms of oppositional defiant disorder (rate and symptom severity P values $< .0001$) and conduct disorder (rate, $P < .0001$; symptom severity, $P = .01$), but did not differ in the rates of mood, anxiety, or attention-deficit/hyperactivity disorders or in severity of inattentive, hyperactive, manic, depressive, or anxiety symptoms. Most of the participants with oppositional defiant disorder (58%) or conduct disorder (61%) met DMDD criteria, but those who were DMDD+ vs DMDD– did not differ in diagnostic comorbidity, symptom severity, or functional impairment. Over 2-year follow-up, 40% of the LAMS sample met DMDD criteria at least once, but 52% of these participants met criteria at only 1 assessment. DMDD was not associated with new onset of mood or anxiety disorders or with parental psychiatric history.

Conclusions: In this clinical sample, DMDD could not be delimited from oppositional defiant disorder and conduct disorder, had limited diagnostic stability, and was not associated with current, future-onset, or parental history of mood or anxiety disorders. These findings raise concerns about the diagnostic utility of DMDD in clinical populations.

J Clin Psychiatry 2012;73(10):1342–1350

© Copyright 2012 Physicians Postgraduate Press, Inc.

Submitted: *January 26, 2012; accepted August 1, 2012 (doi:10.4088/JCP.12m07674).*
Corresponding author: *David Axelson, MD, Western Psychiatric Institute and Clinic, 3811 O'Hara St, Pittsburgh, PA 15213 (axelsonda@upmc.edu).*

Irritable mood and temper outbursts are common in youth referred for psychiatric treatment.[1,2] They are also the core features of the proposed diagnosis disruptive mood dysregulation disorder (DMDD) in *DSM-5*.[3] DMDD is characterized primarily by frequent, severe, recurrent temper outbursts and chronically irritable and/or angry mood, both of which must be present for at least a year. The *DSM-5* Work Groups raised concerns that many youth with severe, nonepisodic irritable mood are inappropriately diagnosed with bipolar disorder.[4] The DMDD diagnosis was constructed to capture the phenomenology of youth with severe, chronic irritability, with the goal of reducing the chance that youth with this phenotype would receive a bipolar diagnosis.

The *DSM-5* Work Groups note that there is currently relatively limited research to support the DMDD diagnosis.[4] Most available studies focus on an overlapping but not identical construct called *severe mood dysregulation* (SMD). SMD includes the core criteria of DMDD, but also requires symptoms of chronic hyperarousal such as insomnia, agitation, distractibility, racing thoughts, flight of ideas, pressured speech, and intrusiveness.[5] Published research on SMD has primarily been from a carefully phenotyped cohort of 146 youth referred to the National Institute of Mental Health (NIMH) Intramural Program.[6] The youth with SMD were predominantly male (66%) and had high lifetime rates of attention-deficit/hyperactivity disorder (ADHD; 85%), oppositional defiant disorder (86%), and anxiety disorders (58%). About 16% met lifetime criteria for major depressive disorder (MDD). The youth with SMD were shown to be different from youth with a specified phenotype of bipolar I disorder (requiring distinct episodes of manic symptoms, including either elated mood or grandiosity) on a number of domains, including lower familial rates of bipolar disorder, lower onset rates of manic and hypomanic episodes over prospective follow-up, and differences on several neuropsychological domains and measures of brain structure and functioning.[6]

Other studies relevant to the SMD/DMDD phenotype have been post hoc analyses of large datasets in which a retrospective diagnosis of SMD was derived from the existing phenotypic variables. In the Great Smoky Mountains Study, 1.8% of the sample met SMD criteria with severe

© 2012 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY OR COMMERCIAL PURPOSES.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

functional impairment, which made it much more common than bipolar disorder (0.1% of the sample).[7] The severely impaired SMD youth from this community sample were predominantly male (66%), but differed from those in the NIMH studies, as only about 32% met criteria for ADHD; 42%, for oppositional defiant disorder; and 21%, for any anxiety disorder. In addition, there was very little longitudinal stability of the SMD diagnosis (83% met SMD criteria at only 1 wave). A retrospective SMD diagnosis was applied to 4 large aggregated community samples and 2 large clinical samples, which were assessed using the NIMH Diagnostic Interview Schedule-IV.[6] Preliminary analyses indicated that in the community samples, 15% of youth with oppositional defiant disorder met SMD criteria, as did about 25% of the youth with oppositional defiant disorder in the clinical samples.

Additional data specific to the DMDD diagnosis are needed; however, given the time constraints involved with the release of the upcoming *DSM-5*, carefully performed prospective studies are not possible. One way to evaluate DMDD is to take data from existing cohorts and retrospectively construct a DMDD diagnosis, similar to what was done for SMD. The Longitudinal Assessment of Manic Symptoms (LAMS) study is one source that can provide suitable data, as participants were sampled from all children presenting for new evaluation at 9 different university-affiliated clinics and were carefully assessed using semistructured interviews.

In order to evaluate the validity of the DMDD diagnosis, it is useful to keep in mind the 5 phases of systematic study proposed by Robins and Guze[8] that are necessary to validate a particular diagnostic classification in psychiatry. Using the LAMS cohort, we can provide relevant data on 4 of these phases: (1) clinical description, (2) delimitation from other disorders, (3) follow-up study, and (4) family study. In this article, we examine the clinical phenomenology of LAMS participants who met a DMDD diagnostic phenotype at intake and evaluate whether the DMDD phenotype can be delimited from other diagnoses, is stable over a 2-year follow-up period, and predicts new onset of *DSM-IV* diagnoses. Lastly, we assess the association of the DMDD phenotype with parental history of different psychiatric disorders.

METHOD

Detailed description of the LAMS study methodology has been published previously.[9,10] The LAMS study screened children presenting for initial psychiatric assessment at 9 outpatient clinics affiliated with 4 academic medical centers: Case Western Reserve University, Cincinnati Children's Medical Center, the Ohio State University, and the University of Pittsburgh Medical Center. The institutional review boards at each site approved all study procedures prior to commencing the study. Parents provided written consent to complete the screening procedure described below. Parents then provided written consent, and children assented to participate in the intake assessment and longitudinal study. The sample was accrued from November 14, 2005, to November 28, 2008.

Clinical Points

- The proposed disruptive mood dysregulation disorder (DMDD) diagnosis is not clearly differentiated from oppositional defiant disorder and conduct disorder in children presenting for psychiatric treatment.
- Youth presenting for treatment with disruptive behavioral, anxiety, and mood disorders will frequently meet the proposed diagnostic criteria for DMDD.
- Many youth with bipolar disorder will meet the primary symptom criteria for DMDD; therefore, careful assessment for manic symptomatology is required for children who present with features of DMDD.

Participant Ascertainment

Parents/guardians of eligible children who were new patients to LAMS outpatient clinics completed the Parent General Behavior Inventory 10-Item Mania Scale (PGBI-10M) to screen for elevated symptoms of mania (ESM).[11] Total scores range from 0 to 30. Each patient whose parent or guardian rated the child at or above a score of 12 (ESM+) was invited to participate in the study. Subsequently, a smaller demographically matched comparison group of patients who scored 11 or lower (ESM–) was also enrolled.

To be eligible, patients must (1) not have received mental health treatment in the LAMS-affiliated outpatient clinics within the past year, (2) be 6–12 years of age, (3) speak English, (4) have an accompanying parent/guardian who speaks English, and (5) not have a sibling or other child in the same household who already participated in the LAMS screening.[9]

The PGBI-10M screen was completed by the parents/guardians of 2,622 children; 1,124 (43%) of the children screened ESM+. Of these, 621 (55%) decided to continue in the next study phases. There were no sociodemographic differences between children/families agreeing to enroll in the longitudinal study and those who did not. ESM–children were sampled with replacement, resulting in inclusion of 86 children without ESM.[9]

Intake Assessment

Diagnoses. Children and their parents/guardians completed the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)[12] with additional depression and manic symptom items derived from the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U K-SADS),[13] as well as items to screen for pervasive developmental disorders. The resulting instrument, the K-SADS-PL-W, is a semistructured interview that assesses current and lifetime psychiatric diagnoses.

© 2012 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

Unmodified *DSM-IV* diagnostic criteria were used, except the criteria for bipolar disorder not otherwise specified (NOS) from the Course and Outcome of Bipolar Youth study[14] were applied: (1) elated mood plus 2 associated symptoms of mania (eg, grandiosity, decreased need for sleep) or irritable mood plus 3 associated symptoms, (2) change in functioning (increase or decrease), (3) the abnormal mood and associated symptoms must be present for a total of at least 4 hours within a 24-hour period, and (4) the participant must have had at least 4 days of meeting the above-noted criteria in his or her lifetime. Bipolar spectrum diagnoses included all participants who met criteria for cyclothymia, bipolar disorder NOS, or bipolar I or II disorder. All diagnoses were reviewed and confirmed by a licensed child psychiatrist or psychologist.

Symptomatic assessment. Mood symptoms were assessed in 2 ways: occurring specifically within the context of a mood episode (ie, "filtered" ratings) and irrespective of association with a distinct change in mood ("unfiltered" ratings). Filtered ratings were quantified using the K-SADS Depression Rating Scale–10 item[15] and the K-SADS Mania Rating Scale[16] constructed from the K-SADS-PL-W mood items. Unfiltered ratings were obtained regarding the past 2 weeks using the Young Mania Rating Scale[17] and the Children's Depression Rating Scale-Revised (CDRS-R).[18,19] As irritability is the primary symptom of the DMDD phenotype, we removed this item from the total scores so that we could look at nonoverlapping mood symptomatology.

Questionnaires assessed dimensions of nonmood symptoms. Parent-reported scores on the ADHD, oppositional defiant disorder, and conduct disorder subscales of the Child and Adolescent Symptom Inventory-4R (CAASI-4R)[20] were examined. The parent-completed Screen for Child Anxiety Related Emotional Disorders (SCARED-P)[21] quantified symptoms of anxiety over the past 6 months.

Functional assessment. Study interviewers completed the Children's Global Assessment Scale[22] to quantify current impairment and most severe level of impairment over the participants' lifetime.

Demographics and school and treatment history. These were obtained by direct interview of the primary caregiver.

Family history. The Family History Screen[23] collected information on psychiatric disorders in the participants' biological parents.

Longitudinal Follow-Up Assessments

The instruments from the intake assessment were repeated every 12 months. However, the time frame for lifetime measures (ie, past psychiatric diagnoses) was for the prior 12 months.

Retrospective DMDD Diagnosis

The operational definition of DMDD used the current ratings of the following items from the K-SADS-PL-W, resulting in criteria closely matching the proposed *DSM-5* criteria.[3]

- ***Severe recurrent temper outbursts.*** This criterion consisted of the "loses temper" item: "severe temper outbursts 2–5 times per week" at threshold.
- ***Chronic irritability.*** This criterion consisted of both the "easily annoyed or angered" ("easily annoyed or angered daily or almost daily") and "angry or resentful" ("angry or resentful daily or almost daily") items at threshold.
- ***Duration.*** Participants who completed the K-SADS-PL-W oppositional defiant disorder supplement were assessed for whether the symptoms were present for at least 6 months, independent of whether they met full criteria for oppositional defiant disorder. This duration differs from DMDD criterion D, which states that symptoms must be present for an interval of 12 or more months and that there cannot be 3 or more consecutive months during the interval when the person was without the symptoms of criteria A–C.
- ***Impairment in more than 1 setting.*** The oppositional defiant disorder supplement determined whether impairment occurred in at least 2 settings.
- ***Episodes of elated mood plus manic-specific symptoms lasting more than 1 day cannot be present.*** DMDD criterion H excludes participants with episodic manic symptoms lasting more than 1 day at a time, thus excluding youth with bipolar I or II disorders and potentially some with bipolar disorder NOS and cyclothymia. However, because whether the DMDD phenotype can be delimited from bipolar disorder (other than by using an exclusion criterion) is a question to be evaluated, participants with bipolar spectrum diagnoses were included in the DMDD group.
- ***Symptoms are not occurring exclusively during a psychotic or mood disorder or are better accounted for by another disorder.*** LAMS interviewers rate symptoms in the oppositional defiant disorder section only if they do not occur exclusively during a psychotic or mood disorder or are clearly accounted for by another disorder.

The proposed *DSM-5* criteria for DMDD specify that individuals meeting criteria for DMDD and oppositional defiant disorder should be given a diagnosis of DMDD. As a goal of these analyses is to evaluate whether DMDD can be delimited from existing *DSM-IV* diagnoses, this criterion was not applied.

One participant did not have complete information on duration and impairment and was excluded from analyses.

Statistical Analyses

Statistical analyses were performed using IBM SPSS version 20.0 (Armonk, New York). Univariate analyses used standard parametric (t, χ^2) or nonparametric (Mann-Whitney U) tests. Multivariate logistic regression models were built with group (eg, DMDD+) as the outcome variable. Variables

© 2012 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY OR COMMERCIAL PURPOSES.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

that had a potential association with the outcome variable at a level of $P<.10$ on the univariate tests were entered using a forward conditional method with $P<.05$ as criteria for entry and $P>.10$ for removal.[24]

For some analyses, participants with oppositional defiant disorder and participants with conduct disorder were pooled (indicated in the article by the phrase *oppositional defiant disorder/conduct disorder*).

RESULTS

Intake Assessment

Severe, recurrent temper outbursts were present in 52% of the LAMS sample, and chronic irritability was present in 35%. The DMDD phenotype was present in 26% (n = 184) of LAMS participants and was significantly more common in the ESM+ vs ESM– participants (28% vs 14%; relative risk [RR] = 1.99; 95% confidence interval [CI], 1.16–3.41; $P=.006$), so ESM status was included as a potential covariate in the multivariate models. An additional 5% (n = 34) of the sample had both severe, recurrent temper outbursts and chronic irritability, but did not meet full criteria for DMDD because they did not have impairment in 2 settings (n = 27), did not meet duration criteria (n = 3), or met neither the impairment nor duration criteria (n = 4).

Table 1 compares the 184 DMDD+ participants with the 522 DMDD– participants on factors measured at intake. DMDD+ participants did not significantly differ from DMDD– participants in the rates of bipolar spectrum diagnoses, any depressive disorders, MDD, or anxiety disorders. DMDD+ participants had higher rates of disruptive behavior disorders, dysthymia, elimination disorders, and ADHD as compared to the DMDD– group. In the multivariate model, only oppositional defiant disorder and conduct disorder remained significantly associated with DMDD (oppositional defiant disorder: Wald $\chi^2=124$, odds ratio [OR] = 68.7 [95% CI, 32.6–144.7], $P<.0001$; conduct disorder: Wald $\chi^2=92$, OR = 77.8 [95% CI, 32.0–189.1], $P<.0001$).

On dimensional measures of psychopathology, DMDD+ youth had significantly higher total scores on the Young Mania Rating Scale, CDRS-R, and K-SADS Mania Rating Scale (all with the irritability item removed), the K-SADS Depression Rating Scale, and the CAASI-4R ADHD subscales and oppositional defiant disorder and conduct disorder scales. On multivariate analysis, only the CAASI-4R oppositional defiant disorder and conduct disorder total scores were significantly associated with DMDD (CAASI-4R oppositional defiant disorder: Wald $\chi^2=45$, OR = 1.16 [95% CI, 1.11–1.21], $P<.0001$; CAASI-4R conduct disorder: Wald $\chi^2=6.1$, OR = 1.05 [95% CI, 1.01–1.10], $P=.01$), along with nonwhite race becoming significantly associated with DMDD in the model (Wald $\chi^2=5.2$, OR = 1.58 [95% CI, 1.07–2.35], $P=.02$).

Youth with DMDD were more impaired than those without DMDD. However, they were not more likely to have repeated a grade, received special educational intervention, taken psychotropic medication, or have a history of inpatient psychiatric hospitalization.

Longitudinal Course

Participants who did not complete any follow-up assessments were less likely to live with both biological parents than those who did complete a follow-up assessment (20% vs 35%); otherwise, there were no significant demographic differences between groups. There were no differences among participants without follow-up versus those with follow-up in the rates of baseline depressive disorders, bipolar spectrum diagnoses, ADHD, anxiety disorders, psychotic disorders, or oppositional defiant disorder/conduct disorder or in baseline DMDD and ESM status.

The 12-month assessment was available for 525 participants (74% of the sample), with 21% meeting DMDD criteria. Of those meeting criteria for DMDD at intake, 53% continued to meet criteria at 12 months. Of the 111 participants who were DMDD+ at the 12-month assessment, 71 (64%) were DMDD+ at intake. For comparison, 85% of participants who met full criteria for ADHD at intake also did so at the 12-month follow-up.

Both 12-month and 24-month follow-up assessments were available in 433 participants (61% of the sample). Of those 433 participants, 172 (40%) met DMDD criteria for at least 1 assessment, including 27% of the ESM– subjects. Of those 172 participants who were DMDD+ at intake or follow-up, 90 (52%) met criteria at only 1 assessment, while 50 (29%) met criteria at 2 assessments and 32 (19%) met criteria for all 3 assessments. In comparison, of the participants who met criteria for ADHD at intake or follow-up, 18% met criteria at only 1 assessment; 21%, at 2 assessments; and 61%, at all 3 assessments.

In participants with both follow-up visits, DMDD at intake was not associated with new onset of bipolar spectrum diagnoses (including bipolar I and II disorders), depressive disorders (including MDD), anxiety disorders, psychotic disorders, or conduct disorder over follow-up (Table 2). A diagnosis of DMDD at either intake or follow-up was significantly associated with a diagnosis at intake or follow-up of oppositional defiant disorder/conduct disorder (71% of those with oppositional defiant disorder/conduct disorder had DMDD vs 3% without oppositional defiant disorder/conduct disorder; $\chi^2=277$, $P<.0001$) and ADHD (44% vs 23%; $\chi^2=20.0$, $P<.0001$), but not MDD (42% vs 38%, $\chi^2=0.4$, $P=.52$), any depressive disorder (44% vs 37%, $\chi^2=2.0$, $P=.16$), bipolar I and II disorders (41% vs 38%; $\chi^2=0.4$, $P=.52$), bipolar spectrum diagnoses (44% vs 36%; $\chi^2=3.1$, $P=.08$), any anxiety disorder (41% vs 38%; $\chi^2=0.4$, $P=.52$), or psychotic disorder (52% vs 38%; $\chi^2=1.9$, $P=.17$).

Distinction From Oppositional Defiant Disorder and Conduct Disorder

At the intake assessment, 58% of youth with oppositional defiant disorder and 61% of youth with conduct disorder

© 2012 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY OR COMMERCIAL PURPOSES.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

Table 1. Factors at Intake by Disruptive Mood Dysregulation Disorder Status

	DMDD+ (n = 184)	DMDD− (n = 522)	Test Statistic/Relative Risk (95% CI)	*P* Value
Demographics				
Sex, male, %	66	68	0.96 (0.86–1.09)	NS
Race, white, %	59	66	0.89 (0.77–1.01)	.06
Age, mean ± SD, y	9.3 ± 1.8	9.5 ± 2.0	$t = 1.2$	NS
Lives with both biological parents, %	28	34	0.84 (0.65–1.09)	NS
Primary caretaker education, %				
No or some high school	13	10	$Z = 1.8$	.08
GED or high school diploma	25	26		
Some post–high school, no degree	30	26		
Associate's degree or other post–high school certification	21	17		
Bachelor's degree or higher	12	21		
Diagnoses, %				
Any mood disorder	44	39	1.13 (0.93–1.37)	NS
Any bipolar spectrum diagnosis	24	23	1.06 (0.78–1.43)	NS
Bipolar I/II disorder	9	11	0.78 (0.46–1.33)	NS
Cyclothymia/bipolar disorder NOS	15	12	1.32 (0.87–2.00)	NS
Any depressive disorder	20	17	1.21 (0.85–1.70)	NS
MDD	7	7	0.92 (0.48–1.73)	NS
Dysthymic disorder	4	2	2.84 (1.09–7.53)	.03
Depressive disorder NOS	9	8	1.15 (0.67–1.97)	NS
Oppositional defiant disorder or conduct disorder	96	24	4.03 (3.44–4.70)	<.0001
Oppositional defiant disorder	78	20	3.94 (3.26–4.77)	<.0001
Conduct disorder	18	4	4.46 (2.66–7.53)	<.0001
ADHD	79	61	1.29 (1.17–1.43)	<.0001
Any anxiety disorder	20	20	0.96 (0.69–1.35)	NS
Psychotic disorder	2	2	1.03 (0.34–3.25)	NS
Pervasive developmental disorder	3	7	0.44 (0.19–1.02)	.04
Elimination disorders	25	18	1.39 (1.02–1.89)	.04
Dimensional measures of psychopathology, mean ± SD				
YMRS total score[a]	15.5 ± 7.7	13.1 ± 8.0	$t = 3.5$	.0004
CDRS-R total score[a]	33.3 ± 9.5	30.6 ± 10.2	$t = 3.2$	.002
K-SADS Depression Rating Scale total score	7.9 ± 5.7	6.6 ± 6.0	$t = 2.6$	.009
K-SADS Mania Rating Scale total score[a]	10.8 ± 8.4	7.7 ± 8.0	$t = 4.4$	<.0001
CAASI-4R subscale score				
ADHD—inattentive	19.5 ± 6.1	17.4 ± 6.7	$t = 3.7$	.0001
ADHD—hyperactive/impulsive	17.9 ± 6.7	15.5 ± 6.9	$t = 4.1$	<.0001
ADHD—combined	37.4 ± 11.3	32.9 ± 12.1	$t = 4.4$	<.0001
Oppositional defiant disorder	19.2 ± 4.5	14.1 ± 6.0	$t = 12.0$	<.0001
Conduct disorder	8.2 ± 5.5	4.5 ± 4.5	$t = 8.2$	<.0001
SCARED-P score	18.2 ± 12.7	18.2 ± 14.1	$t = 0.0$	NS
Functioning				
CGAS score (current), mean ± SD	50.7 ± 9.1	56.0 ± 10.3	$t = 6.6$	<.0001
CGAS score (most severe past), mean ± SD	47.7 ± 10.4	50.1 ± 9.6	$t = 2.3$	.024
Ever repeated a grade, %	16	17	0.96 (0.66–1.41)	NS
Ever received special education class or behavioral intervention in school, %	28	30	0.93 (0.71–1.21)	NS
Lifetime treatment history, %				
Psychotropic medication	59	62	0.95 (0.83–1.09)	NS
Psychiatric hospitalization	10	9	1.18 (0.71–1.96)	NS

[a]Irritability item not included in the total score.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CAASI-4R = Child and Adolescent Symptom Inventory-4R, CDRS-R = Children's Depression Rating Scale-Revised, CGAS = Children's Global Assessment Scale, CI = confidence interval, DMDD− = did not meet criteria for disruptive mood dysregulation disorder, DMDD+ = met criteria for disruptive mood dysregulation disorder, GED = General Equivalency Diploma, K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children, MDD = major depressive disorder, NOS = not otherwise specified, NS = nonsignificant, SCARED-P = Screen for Child Anxiety Related Emotional Disorders, YMRS = Young Mania Rating Scale.

were DMDD+. Nearly all (96%) of DMDD+ youth met criteria for oppositional defiant disorder or conduct disorder (RR vs DMDD− = 4.03 [95% CI, 3.44–4.70]), and 77% met criteria for both ADHD and oppositional defiant disorder/conduct disorder (RR vs DMDD− = 4.30 [95% CI, 3.52–5.26]; Figure 1). In contrast, 41% of participants with MDD (RR vs no MDD = 0.96 [95% CI, 0.68–1.36]) and 40% of those with bipolar spectrum diagnoses (RR vs no bipolar spectrum diagnoses = 0.91 [95% CI, 0.74–1.13]) had comorbid oppositional defiant disorder or conduct disorder; 27% of MDD (RR vs no MDD = 0.79 [95% CI, 0.49–1.27]) and 34% of participants with bipolar spectrum diagnoses (RR vs no bipolar spectrum diagnoses = 1.03 [95% CI, 0.74–1.13]) had both ADHD and oppositional defiant disorder/conduct disorder. There was no difference in the rate of DMDD in participants with oppositional defiant disorder/conduct disorder

© 2012 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY OR COMMERCIAL PURPOSES.
Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

who were ESM+ (59%) versus those that were ESM– (55%; RR = 1.07 [95% CI, 0.71–1.61]). Participants with oppositional defiant disorder/conduct disorder who were DMDD+ did not have significantly different rates of bipolar spectrum diagnoses, depressive disorders, anxiety disorders, or ADHD compared to those who were DMDD– (Table 3). DMDD+ vs DMDD– oppositional defiant disorder/conduct disorder participants did not differ in Young Mania Rating Scale, CDRS-R, K-SADS Depression Rating Scale and K-SADS Mania Rating Scale total scores, CAASI-4R ADHD subscales, SCARED-P total scores, and Children's Global Assessment Scale.

In the participants diagnosed with oppositional defiant disorder or conduct disorder (n = 180) at intake who also had both follow-up assessments, those with DMDD did not differ significantly from those without DMDD in the rates of new onset of bipolar spectrum diagnoses (9% vs 18%; RR = 0.5 [95% CI, 0.21–1.22]), depressive disorders (12% vs 12%; RR = 0.96 [95% CI, 0.39–2.39]), psychotic disorders (3% vs 4%; RR = 0.75 [95% CI, 0.16–3.61]), or anxiety disorders (13% vs 16%; RR = 0.86 [95% CI, 0.39–1.89]).

Parental Psychiatric History

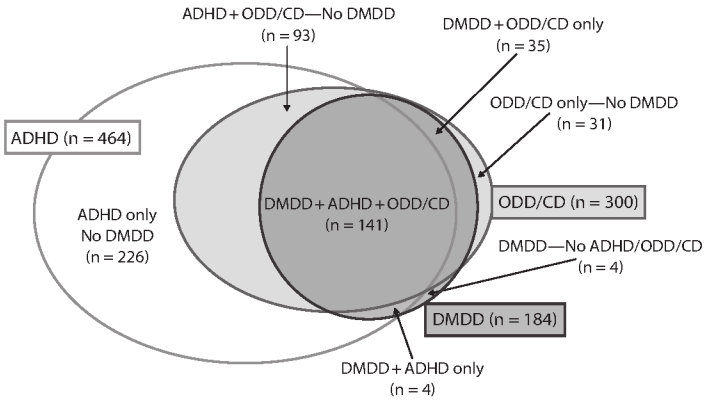
DMDD+ participants at intake did not significantly differ from DMDD– participants in the rates of a screening diagnosis in at least 1 biological parent of depression (DMDD+ 67% vs DMDD– 63%, RR = 1.06 [95% CI, 0.94–1.20]), bipolar disorder (23% vs 20%, RR = 1.19 [95% CI, 0.86–1.66]), anxiety disorder (49% vs 55%, RR = 0.88 [95% CI, 0.74–1.05]), psychotic disorder (14% vs 11%, RR = 1.31 [95% CI, 0.84–2.05]), substance use disorder (48% vs 45%, RR = 1.06 [95% CI, 0.88–1.26]), ADHD (30% vs 26%, RR = 1.12 [95% CI, 0.86–1.47]), or conduct disorder (43% vs 39%, RR = 1.10 [95% CI, 0.90–1.34]).

Table 2. New Onset of Disorder at 12- or 24-Month Follow-Up by Disruptive Mood Dysregulation Disorder Status at Intake, %

Disorder With New Onset at 12 or 24 Mo	DMDD+ at Intake	DMDD– at Intake	Relative Risk (95% CI)	*P* Value
Bipolar spectrum disorder	8.5	10.1	0.84 (0.41–1.70)	NS
Bipolar I/II disorder	5.5	8.0	0.69 (0.31–1.53)	NS
Depressive disorder	11.3	9.1	1.26 (0.68–2.31)	NS
Major depressive disorder	4.7	4.1	1.13 (0.45–2.81)	NS
Anxiety disorder	13.3	9.5	1.40 (0.79–2.48)	NS
Conduct disorder	3.4	2.2	1.55 (0.49–4.94)	NS
Psychotic disorder	2.9	2.2	1.33 (0.42–4.26)	NS

Abbreviations: CI = confidence interval, DMDD– = did not meet criteria for disruptive mood dysregulation disorder, DMDD+ = met criteria for disruptive mood dysregulation disorder, NS = nonsignificant.

Figure 1. Overlap of Disruptive Mood Dysregulation Disorder (DMDD), Attention-Deficit/Hyperactivity Disorder (ADHD), and Oppositional Defiant Disorder (ODD)/Conduct Disorder (CD)



DISCUSSION

The results of these analyses indicate that severe recurrent temper outbursts and chronic irritability are common symptoms in youth presenting for outpatient psychiatric assessment. Moreover, the proposed DMDD diagnosis is common in university child psychiatric outpatient settings. However, DMDD did not identify a phenotype that was clearly differentiated from disruptive behavioral disorders or had a distinct course and outcome, substantial longitudinal stability, or an association with a parental history of mood or anxiety disorders. In comparison to other diagnoses in the LAMS cohort, the degree of overlap between disruptive behavior disorders (oppositional defiant disorder/conduct disorder) and DMDD was far greater than the overlap between oppositional defiant disorder/conduct disorder and mood disorders, and the longitudinal stability of the DMDD diagnosis was far less than the stability of ADHD.

The study results should be considered with regard to the following limitations. The LAMS participants were disproportionately recruited to have elevated PGBI-10M scores, and DMDD was associated with increased PGBI-10M scores. The PGBI-10M has 2 items that assess irritability, although it is in the context of unusually happy mood: (1) periods of feeling unusually happy as well as struggling to control inner feelings of rage and (2) periods of feeling unusually happy when almost everything got on their nerves. Therefore, the sample may not be representative of the cohort of all participants who were screened, which could affect the rates of DMDD and the phenomenology of the DMDD+ participants assessed. However, it is notable that ESM status at baseline was not a significant factor in the multivariate analyses. DMDD criteria were extracted from K-SADS questions so that only a retrospective diagnosis could be applied. The instrument used for ascertaining family history (the Family History Screen) uses a few screening questions to determine diagnoses in family members; these results should be interpreted with caution. The majority of participants presented to outpatient services at academic psychiatry departments, so results may not generalize to other clinical settings or to community samples.

In LAMS, DMDD could not be clearly differentiated from oppositional defiant disorder and conduct disorder. On multivariate assessment, DMDD status at intake was associated

© 2012 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY OR COMMERCIAL PURPOSES.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

Table 3. Factors at Intake by Disruptive Mood Dysregulation Disorder Status in Participants With Oppositional Defiant Disorder or Conduct Disorder

	DMDD+ (n = 176)	DMDD− (n = 124)	Test Statistic/Relative Risk (95% CI)	*P* Value
Demographics				
Sex, male, %	67	74	0.90 (0.78–1.05)	NS
Race, white, %	58	65	0.90 (0.75–1.08)	NS
Age, mean ± SD, y	9.3 ± 1.8	9.5 ± 2.0	$t = 1.2$	NS
Lives with both biological parents, %	28	27	1.05 (0.72–1.52)	NS
Primary caretaker education, %				
No or some high school	13	20	$Z = 1.9$	.06
GED or high school diploma	25	29		
Some post–high school, no degree	29	24		
Associate's degree or other post–high school certification	22	15		
Bachelor's degree or higher	12	12		
Diagnoses, %				
Any mood disorder	42	44	0.94 (0.72–1.22)	NS
Any bipolar spectrum diagnosis	22	20	1.10 (0.70–1.72)	NS
Any depressive disorder	19	24	0.80 (0.52–1.23)	NS
ADHD	80	75	1.07 (0.94–1.21)	NS
Any anxiety disorder	20	22	0.91 (0.58–1.43)	NS
Psychotic disorder	2	3	0.53 (0.12–2.32)	NS
Pervasive developmental disorder	3	1	4.23 (0.52–34.7)	NS
Dimensional measures of psychopathology, mean ± SD				
YMRS total score[a]	15.5 ± 7.8	15.0 ± 7.6	$t = 0.6$	NS
CDRS-R total score[a]	33.1 ± 9.5	32.3 ± 10.3	$t = 0.7$	NS
K-SADS Depression Rating Scale total score	7.8 ± 5.7	7.1 ± 5.9	$t = 1.0$	NS
K-SADS Mania Rating Scale total score[a]	10.6 ± 8.3	8.8 ± 7.8	$t = 1.9$	.06
CAASI-4R subscale score				
ADHD—inattentive	19.6 ± 6.0	18.4 ± 6.3	$t = 1.7$	NS
ADHD—hyperactive/impulsive	18.1 ± 6.6	17.3 ± 6.5	$t = 1.0$	NS
ADHD—combined	37.7 ± 11.1	35.7 ± 11.5	$t = 1.5$	NS
SCARED-P score	17.8 ± 12.4	17.3 ± 12.4	$t = 0.3$	NS
Functioning, mean ± SD				
CGAS score (current)	50.8 ± 9.2	51.5 ± 10.3	$t = 0.6$	NS
CGAS score (most severe past)	48.1 ± 10.3	46.1 ± 10.3	$t = 1.3$	NS

[a]Irritability item not included in the total score.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CAASI-4R = Child and Adolescent Symptom Inventory-4R, CDRS-R = Children's Depression Rating Scale-Revised, CGAS = Children's Global Assessment Scale, CI = confidence interval, DMDD− = did not meet criteria for disruptive mood dysregulation disorder, DMDD+ = met criteria for disruptive mood dysregulation disorder, GED = General Equivalency Diploma, NS = nonsignificant, SCARED-P = Screen for Child Anxiety Related Emotional Disorders, YMRS = Young Mania Rating Scale.

only with oppositional defiant disorder and conduct disorder diagnoses, and these associations were not affected by ESM status. At intake, the majority of youth with oppositional defiant disorder (59%) or conduct disorder (61%) also met criteria for DMDD. These percentages are substantially higher than those found in some clinical cohorts, where approximately 25% of the oppositional defiant disorder participants met DMDD criteria.[6] However, a clinical sample from a recent treatment study[25] had similar levels of overlap of SMD with oppositional defiant disorder and conduct disorder, as 44% of participants with oppositional defiant disorder and 67% of those with conduct disorder met SMD criteria. The oppositional defiant disorder/conduct disorder youth with DMDD did not differ from those without DMDD in age, sex, rates of comorbid disorders or of onset of new disorders over follow-up, dimensional psychopathology, or functional impairment. The degree of diagnostic overlap between DMDD and oppositional defiant disorder/conduct disorder (RR = 4.0) was many orders of magnitude greater than for other mood disorders in the sample such as MDD or bipolar spectrum diagnoses, both of which were not significantly associated with oppositional defiant disorder/conduct disorder (RR, 0.9–1.0).

DMDD was not specifically associated with disorders other than oppositional defiant disorder and conduct disorder, although DMDD was present in 40%–50% of youth diagnosed with anxiety, depressive, and bipolar spectrum disorders during the first 2 years of the study. On multivariate analysis, DMDD was associated with dimensional psychopathology only in the domains of disruptive behavior disorders. DMDD at intake did not specifically predict future onset of mood or anxiety disorders over follow-up. Finally, DMDD was not associated with a parental history of ADHD or mood, anxiety, conduct, or substance use disorders. These findings stand in contrast to results from epidemiologic studies,[7,26–28] which found that chronic irritability (including SMD) in childhood was associated with future onset of depressive and anxiety disorders.

Multiple factors may contribute to the disparate findings. Participant ascertainment may play a key role, as there are potential differences in the phenomenology of depressed and DMDD youth who are seeking treatment and enriched

© 2012 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY OR COMMERCIAL PURPOSES.

for the presence of manic symptomatology versus those in the community. In addition, epidemiologic samples would be expected to have much lower rates of DMDD and mood disorders in general, and bipolar disorder in particular, than the LAMS sample. Low numbers of participants with bipolar disorder can lead to difficulty in obtaining accurate estimates of the association of DMDD with bipolarity. Operationalization of the retrospective diagnoses could affect results, as some studies[7,28] included irritability items drawn from the depression section of the assessment, which could increase the association of DMDD and later depression. Age of the participants and the duration of follow-up could also influence the findings. The LAMS cohort was 9½ years old on average at intake and was followed for only 2 years to date, so they were well before the maximum age of risk for onset of depression or bipolar disorder at the end of follow-up. In contrast, the epidemiologic studies often followed participants into young adulthood.[7,26] These differences in methodology reinforce the need for multiple studies (preferably with repeated assessment and extended longitudinal follow-up) using different sampling and assessment strategies, to determine whether a clearer consensus on DMDD can emerge.

DMDD was not associated with bipolar disorder overall, or with a family history of manic symptoms. This lack of association lends support to the conceptualization that *chronic* irritability and temper outbursts are not specific manifestations of pediatric bipolar disorder. However, given that 44% of youth with bipolar I or II disorder would have met criteria for DMDD except for the bipolar diagnostic exclusion, clinicians will need to carefully assess for the presence of manic symptomatology in youth who have the DMDD phenotype, or children who actually have bipolar disorder could be mislabeled as having DMDD.

In the LAMS cohort, DMDD was a common but somewhat transient phenotype that could not be clearly differentiated from disruptive behavior disorders (oppositional defiant disorder and conduct disorder) and was otherwise not specifically associated with other diagnoses or symptom domains. These findings indicate that additional research will be required to clarify whether the DMDD phenotype is a valid, separate diagnostic entity.

Author affiliations: Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, University of Pittsburgh, Pittsburgh, Pennsylvania (Drs Axelson, Ryan, and Birmaher and Ms Gill); Department of Psychiatry, Division of Child and Adolescent Psychiatry, Case Western Reserve University, Cleveland (Dr Findling and Mss Demeter, Kennedy, Gron, and Rowles); Department of Psychiatry, Division of Child and Adolescent Psychiatry, Ohio State University, Columbus (Drs Fristad, Arnold, and Hauser-Harrington); Division of Psychiatry, Cincinnati Children's Hospital Medical Center, Cincinnati (Dr Kowatch and Ms Depew), Ohio; Department of Psychology, University of North Carolina at Chapel Hill (Dr Youngstrom); Department of Pediatrics and Stanford Health Policy, Stanford University School of Medicine, Stanford, California (Dr Horwitz); and Center for Pediatric Behavioral Health and Center for Autism, Cleveland Clinic, Cleveland, Ohio (Dr Frazier).

Potential conflicts of interest: **Dr Findling** receives or has received research support from, acted as a consultant for, received royalties from, and/or served on a speakers bureau for Abbott, Addrenex, Alexza, American Psychiatric Press, AstraZeneca, Biovail, Bristol-Myers Squibb, Dainippon Sumitomo, Forest, GlaxoSmithKline, Guilford Press, Johns Hopkins University Press, Johnson & Johnson, KemPharm, Eli Lilly, Lundbeck, Merck, National Institutes of Health, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Physicians Postgraduate Press, Rhodes, Roche, Sage, Sanofi-Aventis, Schering-Plough, Seaside Therapeutics, Sepracor, Shionogi, Shire, Solvay, Stanley Medical Research Institute, Sunovion, Supernus, Transcept, Validus, WebMD, and Wyeth. **Dr Fristad** receives royalties from Guilford Press, American Psychiatric Publishing, and CFPSI Press. **Dr Kowatch** receives or has received research support from, acted as a consultant for, and/or served on a speakers bureau for Forest, AstraZeneca, *Current Psychiatry*, and the REACH Foundation. **Dr Youngstrom** has received travel support from Bristol-Myers Squibb and consulted with Lundbeck. **Dr Arnold** receives or has received research support from, acted as a consultant for, and/or served on a speakers bureau for Abbott, AstraZeneca, Biomarin, Celgene, Curemark, Eli Lilly, McNeil, Novartis, Noven, Neuropharm, Organon, Shire, Sigma Tau, and Targacept. **Dr Frazier** has received federal funding or research support from, acted as a consultant to, received travel support from, and/or received a speaker's honorarium from Forest, Ecoeos, IntegraGen, Shire, Bristol-Myers Squibb, National Institutes of Health, and the Brain and Behavior Research Foundation. **Dr Birmaher** receives or has received research support from and acted as a consultant for Schering Plough. He receives royalties from Random House and Lippincott Williams & Wilkins and support from NIMH. **Drs Axelson**, **Horwitz**, **Ryan**, and **Hauser-Harrington**; **Mss Demeter**, **Gill**, **Depew**, **Gron**, and **Rowles**; and **Mr Kennedy** report no potential conflict of interest.

Funding/support: This study was supported by the National Institute of Mental Health (R01-MH073967, R01-MH073801, R01-MH073953, R01-MH073816).

Disclaimer: The authors acknowledge that the findings and conclusions presented in this paper are those of the authors alone and do not necessarily reflect the opinions of NIMH.

Acknowledgment: The authors thank the National Institute of Mental Health for their support.

REFERENCES

1. Bambauer KZ, Connor DF. Characteristics of aggression in clinically referred children. *CNS Spectr*. 2005;10(9):709–718.
2. Carlson GA, Potegal M, Margulies D, et al. Rages: what are they and who has them? *J Child Adolesc Psychopharmacol*. 2009;19(3):281–288.
3. D 00 Disruptive mood dysregulation disorder. American Psychiatric Association *DSM-5* Development. http://www.dsm5.org/ProposedRevision/Pages/proposedrevision.aspx?rid=397. Updated April 2012. Accessed August 9, 2012.
4. Issues pertinent to a developmental approach to bipolar disorder in DSM-5. http://www.dsm5.org/Proposed%20Revision%20Attachments/APA%20Developmental%20Approaches%20to%20Bipolar%20Disorder.pdf. Updated 2010. Accessed August 9, 2012.
5. Leibenluft E, Charney DS, Towbin KE, et al. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry*. 2003;160(3):430–437.
6. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am J Psychiatry*. 2011;168(2):129–142.
7. Brotman MA, Schmajuk M, Rich BA, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biol Psychiatry*. 2006;60(9):991–997.
8. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry*. 1970;126(7):983–987.
9. Horwitz SM, Demeter CA, Pagano ME, et al. Longitudinal Assessment of Manic Symptoms (LAMS) study: background, design, and initial screening results. *J Clin Psychiatry*. 2010;71(11):1511–1517.
10. Findling RL, Youngstrom EA, Fristad MA, et al. Characteristics of children with elevated symptoms of mania: the Longitudinal Assessment of Manic Symptoms (LAMS) study. *J Clin Psychiatry*. 2010;71(12):1664–1672.
11. Youngstrom EA, Frazier TW, Demeter C, et al. Developing a 10-item mania scale from the Parent General Behavior Inventory for children and adolescents. *J Clin Psychiatry*. 2008;69(5):831–839.
12. 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.

© 2012 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY OR COMMERCIAL PURPOSES.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

J Am Acad Child Adolesc Psychiatry. 1997;36(7):980–988.
13. Geller B, Zimerman B, Williams M, et al. Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. *J Am Acad Child Adolesc Psychiatry*. 2001;40(4):450–455.
14. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*. 2006;63(10):1139–1148.
15. Chambers WJ, Puig-Antich J, Hirsch M, et al. The assessment of affective disorders in children and adolescents by semistructured interview: test-retest reliability of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present Episode Version. *Arch Gen Psychiatry*. 1985;42(7):696–702.
16. Axelson D, Birmaher BJ, Brent D, et al. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale for children and adolescents. *J Child Adolesc Psychopharmacol*. 2003;13(4):463–470.
17. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
18. Overholser JC, Brinkman DC, Lehnert KL, et al. Children's Depression Rating Scale-Revised: development of a short form. *J Clin Child Psychol*. 1995;24(4):443–452.
19. Poznanski EO, Grossman JA, Buchsbaum Y, et al. Preliminary studies of the reliability and validity of the Children's Depression Rating Scale. *J Am Acad Child Psychiatry*. 1984;23(2):191–197.
20. Gadow KD, Sprafkin J. *Child and Adolescent Symptom Inventory-4R*. Stony Brook, NY: Checkmate Plus; 2005.
21. Birmaher B, Khetarpal S, Brent D, et al. The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. *J Am Acad Child Adolesc Psychiatry*. 1997;36(4):545–553.
22. Shaffer D, Gould MS, Brasic J, et al. A Children's Global Assessment Scale (CGAS). *Arch Gen Psychiatry*. 1983;40(11):1228–1231.
23. Weissman MM, Wickramaratne P, Adams P, et al. Brief screening for family psychiatric history: the Family History Screen. *Arch Gen Psychiatry*. 2000;57(7):675–682.
24. Hosmer DW, Lemeshow S. In: Shewhart WA, Wilks SS, eds. *Applied Logistic Regression*. New York, NY: Wiley & Sons, Inc. 2000.
25. Waxmonsky J, Pelham WE, Gnagy E, et al. The efficacy and tolerability of methylphenidate and behavior modification in children with attention-deficit/hyperactivity disorder and severe mood dysregulation. *J Child Adolesc Psychopharmacol*. 2008; 18(6):573–588.
26. Stringaris A, Cohen P, Pine DS, et al. Adult outcomes of youth irritability: a 20-year prospective community-based study. *Am J Psychiatry*. 2009;166(9):1048–1054.
27. Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: irritable, headstrong, and hurtful behaviors have distinctive predictions. *J Am Acad Child Adolesc Psychiatry*. 2009; 48(4):404–412.
28. Leibenluft E, Cohen P, Gorrindo T, et al. Chronic versus episodic irritability in youth: a community-based, longitudinal study of clinical and diagnostic associations. *J Child Adolesc Psychopharmacol*. 2006;16(4):456–466.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

© 2012 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY OR COMMERCIAL PURPOSES.
Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

FOCUS ON CHILDHOOD AND ADOLESCENT MENTAL HEALTH
COMMENTARY

Concerns Regarding the Inclusion of Temper Dysregulation Disorder With Dysphoria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition

David A. Axelson, MD; Boris Birmaher, MD; Robert L. Findling, MD; Mary A. Fristad, PhD; Robert A. Kowatch, MD; Eric A. Youngstrom, PhD; L. Eugene Arnold, MD, MEd; Benjamin I. Goldstein, MD, PhD; Tina R. Goldstein, PhD; Kiki D. Chang, MD; Melissa P. DelBello, MD; Neal D. Ryan, MD; and Rasim S. Diler, MD

Though we understand the incredibly difficult work required in order to revise the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) and appreciate the efforts of those serving to develop it, we as a group are strongly against including temper dysregulation disorder with dysphoria (TDD) as an official diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*). We believe that currently there is insufficient scientific support to include TDD as a unique diagnostic entity. Furthermore, we believe that the inclusion of TDD will have an adverse impact on patient care, research, and the general public's perception of child psychiatry. Our concerns are outlined below, and then we offer some alternative strategies to improve diagnostic classification of chronically irritable youths for the *DSM-5* Work Groups to consider.

Of utmost concern is the fact that the TDD diagnosis, as currently conceived, does not have symptom criteria that are specific to TDD as a syndrome. The TDD diagnosis rests on 2 primary criteria: recurrent severe temper outbursts and chronically irritable and/or sad mood. As temper outbursts are a behavioral manifestation of irritable mood, the diagnosis of TDD as it is currently proposed, can be fulfilled with the presence of a single symptom. However, the symptom of irritability is a *DSM-IV* diagnostic criterion for a range of psychiatric disorders in children and adolescents that span the mood, anxiety, and disruptive behavior disorder categories: bipolar disorder, major depressive disorder, dysthymic disorder, cyclothymic disorder, generalized anxiety disorder, posttraumatic stress disorder, acute stress disorder, and oppositional defiant disorder (ODD). In addition, irritability (with temper outbursts) is commonly present in other disorders such as attention-deficit/hyperactivity disorder (ADHD), conduct disorder, separation anxiety disorder, autism spectrum disorders, reactive attachment disorder, psychotic disorders, and substance use disorders and in children who have been maltreated or abused or those who have suffered brain injury from trauma, developmental insults, or in utero exposure to drugs or alcohol. All of these other disorders have multiple additional criteria that provide specificity to the different syndromes. Temper dysregulation disorder with dysphoria does not have other symptoms or criteria that are unique to the TDD diagnosis. The symptoms of hyperarousal from the severe mood dysregulation (SMD) criteria of Leibenluft et al, 2003,[1] are not required in the proposed criteria. The mood criteria for TDD of chronically irritable and/or sad mood more days than not lasting for at least 1 year's duration are nearly identical to those for dysthymic disorder. The TDD criteria rely on warnings to differentiate TDD from mood and anxiety disorders, and they explicitly allow for comorbidity with disruptive behavior and substance use disorders. The requirement of persistence and chronicity in the TDD criteria is not different from many other disorders in which irritability is common, and the severity of irritability as conceptualized in TDD does not preclude diagnosing these disorders, which are known to have continua of severity. This raises the question as to whether TDD is a separate diagnostic entity that is likely to have unique pathophysiologic features or whether its creation is conflating a symptom with a psychiatric syndrome.

In fact, excerpts from the reports written by the *DSM-5* Child and Adolescent Disorders and Mood Disorders Work Groups confirm that the scientific evidence for creating TDD as a new disorder separate from ODD is currently lacking:

> …[T]he work groups acknowledged that a stronger case could be made, based purely on the scientific evidence, for placing the TDD syndrome within the diagnosis of ODD, as a specifier, as opposed to adding a new, free-standing, TDD diagnosis, since virtually all youths who meet criteria for TDD will also meet criteria for ODD. Specifically, data analyses performed by the Childhood and Adolescent Disorders Work Group, using data sets from both community-based and clinic-based samples including more than 10,000 children, suggest that approximately 15% of patients with ODD would meet criteria for TDD; by definition, essentially all youths meeting criteria for TDD would also meet criteria for ODD. In that sense, it is clear that, from a pathophysiological perspective, TDD is unlikely to be categorically distinct from ODD…[2(p7)]

Submitted: May 4, 2010; accepted October 5, 2010.
Online ahead of print: May 3, 2011 (doi:10.4088/JCP.10com06220).
Corresponding author: David A. Axelson, MD, Western Psychiatric Institute and Clinic, 3811 O'Hara St, Pittsburgh, PA 15213 (axelsonda@upmc.edu).
J Clin Psychiatry 2011;72(9):1257–1262.
© Copyright 2011 Physicians Postgraduate Press, Inc.

© Copyright 2011 Physicians Postgraduate Press, Inc. © Copyright 2011 Physicians Postgraduate Press, Inc.
Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801-5215

The fact that TDD is unlikely to be categorically distinct from ODD is a persuasive reason not to include it as a distinct diagnosis in the *DSM-5*. It also suggests that a substantial amount of additional research will be required until there is sufficient evidence to create a new diagnostic entity focused on irritability as a primary symptom that will have meaningful differences in phenomenology, course, and response to treatment from existing diagnoses in the *DSM-IV* such as ODD.

As noted in the *DSM-5* Task Force document "Justification for Temper Dysregulation Disorder With Dysphoria," the scientific support for the TDD diagnosis is limited, and it emerges primarily from one research group.[3] This fact in itself is problematic, as replication by independent research teams is a requirement for establishing the scientific validity of research findings. Recently in psychiatry we have repeatedly seen the lack of replication of genetic and neuroimaging findings across different research groups. In addition, the studies that do have bearing on TDD do not examine it directly but instead focus on an overlapping but not identical population of youths with SMD. Although the outstanding research on SMD from the National Institute of Mental Health (NIMH) Intramural Group is groundbreaking, and it demonstrates that a subset of youths with severe, chronic irritability does not have bipolar disorder, it is not sufficient to justify inclusion of a new TDD diagnostic category. Careful comparison of the original SMD definition proposed in 2003 with the definitions used in subsequent data articles reveals several changes, and the proposed TDD definition makes additional changes, including (1) omitting the hyperarousal criteria and (2) relaxing most of the exclusion criteria, including substance use, low cognitive ability, or comorbid disruptive behavior disorders. It is crucial that both of these changes be evaluated empirically, because they are likely to have substantial impact on the rates of comorbidity and prevalence of the new diagnostic category.

The studies from the NIMH Intramural Group contrasting youths with SMD with those with a narrow phenotype of bipolar I disorder used highly distilled samples of rigorously screened subjects from families who had the motivation to travel to the NIMH campus. This strategy is entirely appropriate for pursuing the initial stages of research to identify potential pathophysiological differences between phenotypic groups. However, it is of questionable applicability to the TDD diagnostic category as it applies in more general clinical and community settings.

The contrast between the SMD subjects recruited at the NIMH Intramural Campus and subjects identified as having SMD in an epidemiologic sample highlights the problems of translating criteria developed from highly distilled samples to community samples. The SMD subjects from the Intramural studies had extremely high rates of comorbid anxiety disorders (47%–61%), ODD (83%–84%), and ADHD (80%–94%).[4,5] In order to examine SMD in large community samples, the SMD criteria were also applied retrospectively to the sample from the Great Smoky Mountains Study (GSMS).[6] The subjects from the GSMS who were identified as having SMD were clearly different from the SMD subjects in the NIMH research samples. Even in the subset of SMD subjects deemed severely impaired (about 1.8% of the total GSMS sample), only about 32% met criteria for ADHD, 42% for ODD, and 21% for any anxiety disorder. In addition, there was very little longitudinal stability of the SMD diagnosis in the GSMS subjects (83% met SMD criteria at only 1 wave), despite the fact that SMD is a chronic disorder that requires a minimum duration of 1 year. We are not aware of published studies that prospectively applied SMD criteria to general clinical populations; therefore, we have no data on the phenomenology, course, or neurobiology of youths meeting the SMD criteria from the most relevant population for the *DSM-5*.

Further complicating the applicability of the published research on SMD to the TDD diagnosis is the removal of the SMD hyperarousal criteria. The rationale for this step was that, since the vast majority of SMD youths had comorbid ADHD, these symptoms when present would be indicated by the ADHD. However, one reason for the high rates of SMD-ADHD comorbidity may be the required hyperarousal criteria. Application of the proposed TDD criteria to general clinical populations might result in much lower rates of ADHD, and it would likely result in children and adolescents diagnosed with TDD who have only some features in common with the SMD subjects studied by the NIMH Intramural Group. Therefore very little research exists that has direct applicability to the TDD diagnosis, and the limited data that do have relevance to TDD have been produced by only one research group.

We suggest that the *DSM-5* Work Groups give additional consideration to the potential risks of introducing the TDD diagnosis. As noted above, the proposed TDD criteria will likely identify a broader range of patients when applied in clinical settings. Irritability and temper outbursts are among the most common presenting complaints in child and adolescent psychiatry. Since TDD has these as its primary diagnostic criteria without any other accompanying symptoms, it could readily become the default diagnosis for the vast majority of children presenting with these symptoms. It will be the responsibility of the diagnosing clinician to determine whether the exclusion criteria (no bipolar disorder; not occurring exclusively during a mood or anxiety disorder; not better accounted for by another diagnosis such as PTSD or pervasive developmental disorder) are present or not. However, it will take considerable effort to evaluate the exclusion criteria, and it is not at all clear that clinicians or research diagnosticians will be able to reliably determine whether the irritability and temper outbursts occur exclusively during a mood or anxiety disorder or whether they are better accounted for by another disorder. It will be easier to assign the TDD diagnosis, rather than to contend with the underlying depression, ADHD, anxiety, or bipolar disorder. We have already seen this play out with the SMD designation in consultations with colleagues from the United States

© Copyright 2011 Physicians Postgraduate Press, Inc. © Copyright 2011 Physicians Postgraduate Press, Inc.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

and other countries—children who have clear episodes of mania and/or hypomania have been given a diagnosis of SMD because of the presence of intense irritability and a reluctance to use a bipolar diagnosis in a child.

The treatment implications of a TDD diagnosis are unclear. Reports in the media have noted that the primary benefit of the TDD diagnosis will be that fewer children will be diagnosed with bipolar disorder, which would lead to fewer children exposed to antipsychotics and mood stabilizers.[7,8] Some media commentaries have implied that youths with TDD will instead receive psychosocial treatments, which would be a more appropriate outcome.[9] However, we know little about what kinds of psychosocial treatments would help youths diagnosed with TDD or whether psychosocial treatment would work at all. At present, there are no published studies of psychosocial treatments for TDD. In addition, to the extent that having the TDD diagnosis may encourage clinicians to inappropriately ignore diagnosis and treatment of ADHD and autism spectrum, anxiety, or mood disorders, psychiatrically ill youths will be denied medications that have been proven to treat these disorders. As these other disorders have very different pharmacologic treatments (eg, stimulants and α_2 antagonists for ADHD, serotonin selective reuptake inhibitors for anxiety disorders, second-generation antipsychotics for irritability in autism spectrum disorders) and psychosocial interventions (cognitive-behavioral therapy for anxiety disorders, intensive behavior interventions for autism spectrum disorders, and Parent Management Training for ADHD youths with oppositionality), the clinical application of TDD may result in more frequent mismatches between individual patients and evidence-based treatments.

On the other hand, the rationale that TDD will reduce the inappropriate use of medication in children and adolescents with temper outbursts also seems at odds with perceptions of how the pharmaceutical industry approaches the *DSM*. Official diagnostic status in *DSM-5* will allow TDD to become a target for pharmaceutical companies to obtain US Food and Drug Administration (FDA) indication for the treatment of TDD. Clinical experience and prior studies indicate that youths with conduct disorder and/or explosive aggression will have short-term clinical improvement when treated with antipsychotics and mood stabilizers.[10–14] The majority of youths who participated in these studies would have likely met the proposed TDD criteria. It is eminently possible that FDA registration studies of new antipsychotics would show an efficacy signal for TDD in short-term treatment. There may be subsets of youths who would meet rigorously assessed TDD diagnostic criteria for whom antipsychotic treatment may indeed be the treatment of choice. However, given the concerns noted above about the application of TDD in clinical settings resulting in identification of a much larger, heterogeneous group of children and adolescents who have other primary diagnoses, there will almost certainly be many youths diagnosed with TDD for whom antipsychotics would not be appropriate. Instead of reducing the use of antipsychotics in youths, which was specified as a potential benefit of the TDD diagnosis by some media reports, it is quite possible that it will serve as justification for expanding antipsychotic use to a much broader range of children, many of whom might respond as well or better to psychosocial interventions or pharmacologic treatments targeted for ADHD, anxiety, or depression.

Adding the TDD diagnosis to *DSM-5* will almost certainly have an adverse effect on the general public's perception of child psychiatry. The media is rife with charges that psychiatry pathologizes normal behavior and turns misbehavior and character flaws into medical disorders, thereby absolving individuals from responsibility for their actions. Skeptical and humorous reports have already surfaced in the media about how temper outbursts in children are now going to be classified as a disease and that the *DSM-5* will have a "temper-tantrum" disorder. The *DSM-5* Work Groups' acknowledgment that there is insufficient scientific basis to establish TDD as a separate diagnosis will further undermine the public's confidence that psychiatry as a discipline uses scientific evidence to support diagnosis and treatment.

The overarching reason for the creation of a separate TDD diagnosis given by the *DSM-5* Child and Adolescent Disorders and Mood Disorders Work Groups was clinical necessity driven by the perceived marked overdiagnosis of bipolar disorder in youth. Although *DSM-5* may be able to play some role in improving the diagnosis of bipolar disorder in youth, we believe that creation of a new, unsubstantiated diagnosis in order to prevent misapplication of a different diagnosis is misguided and a step backward for the progression of psychiatry as a rational scientific discipline. It is trying to solve one problem by creating another, potentially larger problem. Diagnosing bipolar disorder in youth can be very difficult, and misdiagnosis certainly occurs. As research clinicians who specialize in the assessment of youths with possible bipolar disorder, we have certainly seen many referrals of youths with chronic irritability who have been inappropriately assigned a diagnosis of bipolar disorder. The degree to which bipolar disorder is misdiagnosed in community treatment settings remains an empirical question. Existing research relies on diagnostic information culled from insurance claim databases, and there are multiple factors that influence why a diagnosis is placed on third-party payer claims. In addition, the most prominently cited study used the documented rate of bipolar disorder placed on claims for *individual office visits* over a 1-year period, not the rate of *individual patients diagnosed* with bipolar disorder, and the findings revealed an increase from a very low base rate of 0.025%–1% over the time period studied.[15] Given that the most recent psychiatric epidemiologic study of adolescents in the United States found that the combined rate of bipolar I and II disorders was 2.3%,[16] it is difficult to interpret these results as evidence of marked overdiagnosis. Additional studies will be required to answer this question.

© Copyright 2011 Physicians Postgraduate Press, Inc. © Copyright 2011 Physicians Postgraduate Press, Inc.

We agree with the concern raised by the *DSM-5* Work Groups that youths with chronic irritability and explosive anger outbursts are not adequately served by the current *DSM-IV* classification system and that there are children and adolescents with this symptom presentation who are being misdiagnosed as having bipolar disorder. A major problem is that there are surprisingly few data to guide decisions regarding diagnostic classification of these youths. The complexities surrounding the conceptualization and measurement of irritability as a symptom of psychopathology in youths and the assessment and treatment of youths who have chronic explosive irritable mood should be a major focus of future research.

The diagnostic accuracy of bipolar disorder in youth can be improved through better education about rigorously applying current criteria for manic, mixed, or hypomanic *episodes* and ongoing research into the phenomenology, neurobiology, and longitudinal course of youths who present with symptoms of bipolar disorder that do not meet the *DSM* threshold for bipolar I or II disorders. Research into different subthreshold phenotypes that may be part of the bipolar spectrum or may be the early signs and symptoms of bipolar disorder will allow for a scientifically informed, developmentally appropriate, iterative refinement of the *DSM* criteria for bipolar disorder. Creating the TDD diagnostic category would likely lump together a very heterogeneous group of youths, including some who truly have bipolar disorder. This would not improve psychiatric diagnosis in children and adolescents.

The most conservative option available to the *DSM-5* is not to make any changes in regard to the area of irritability in youth and pediatric bipolar disorder, and this would be preferable to creating the TDD diagnosis. However, we recognize that there is a pressing clinical need to identify and better diagnose those children and adolescents with severe irritability who do not have bipolar disorder. We believe that there are viable alternative options for the *DSM-5* that could address this need and facilitate new research that are preferable to establishing TDD as a stand-alone disorder.

One option would be to establish a TDD-like (using an alternative name such as *with severe explosive anger outbursts*) course specifier for other diagnoses (such as ODD, ADHD, conduct disorder, autism spectrum disorders, mood disorders, and anxiety disorders). The course specifier has considerable appeal. A course specifier focusing exclusively on the presence of severe explosive anger outbursts across a wide range of existing *DSM* diagnoses would highlight the clinical significance of this symptom. It would also facilitate research into whether the presence of severe explosive anger outbursts is a major determinant of course and outcome.

For instance, ODD, as currently defined, is a highly heterogenous condition that leads to a wide variety of longitudinal outcomes.[17,18] Adding a course specifier would facilitate research into whether the presence of severe explosive anger outbursts identifies a treatment-relevant subtype of ODD that has meaningful differences in pathophysiology and longitudinal phenomenology from other youths with ODD. Similar research questions could be addressed in regard to explosive anger outbursts in the context of mood disorders, ADHD, and anxiety disorders. Research studies could examine the prognostic and pathophysiological significance of severe explosive anger outbursts independent of the primary *DSM* diagnosis. Having a course specifier would also provide a separate diagnostic code indicative of additional symptomatology and severity that could facilitate reimbursement from third-party payers.

There are limitations to the course specifier option. It could be cumbersome to implement. There would be valid questions as to whether it should be reserved for use in children and adolescents or also used in adults. It could have impact on the usefulness of the current *DSM-IV* diagnosis of intermittent explosive disorder. However, even if TDD were included as a new disorder, it would substantially overlap with intermittent explosive disorder. There is little research supporting the implementation of the specifier across many diagnoses, although the co-occurrence of severe explosive anger outbursts with mood, anxiety, autism spectrum, and disruptive behavior disorders is widely recognized by clinicians. Moreover, the NIMH Intramural SMD research applies to ADHD, MDD, and anxiety disorders almost as much as ODD, given the presence of these comorbidities in the samples.

Another option would be to include an analog of SMD as a separate diagnosis for further study in the *DSM-5* Appendix. The diagnosis for further study could be based on the SMD criteria, including chronic irritability, anger outbursts, dysphoria, and symptom clusters hypothesized to be specific to the SMD syndrome. The SMD-like diagnosis would facilitate research into a more specific phenotype than would the *severe explosive anger outbursts* course specifier. Additional research could clarify and confirm that youths who meet diagnostic criteria for this diagnosis have pathophysiology, family history, longitudinal course, and treatment response that differs from those with existing *DSM* diagnoses.

Note that these 2 options are not mutually exclusive. The *with severe explosive anger outbursts* course specifier could address current clinical needs and certain types of research questions. The SMD-like diagnosis for further study would facilitate research into a phenotype that, with further evidence and refinement, could become a stand-alone diagnosis in the future.

We would recommend against including a TDD-like course specifier for only ODD. This would likely result in problems similar to those posed by having a stand-alone TDD diagnosis. Clinicians could lump a broad, heterogeneous group of severely irritable youths into a diagnosis of ODD + TDD, neglecting to consider the diagnosis of other disorders. Similar issues would exist regarding targeting this heterogeneous group for new pharmacologic FDA indications that might be appropriate for only a small subset who would receive the ODD + TDD diagnosis in clinical

© Copyright 2011 Physicians Postgraduate Press, Inc. © Copyright 2011 Physicians Postgraduate Press, Inc.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801

settings. The situation might not be as problematic as one created by a stand-alone TDD diagnosis, as clinicians are used to applying comorbid diagnoses to ODD (eg, ODD and generalized anxiety disorder), but it still might create substantial problems.

The *DSM-5* should also address the issue of bipolar disorder in youth within the Mood Disorders section of the manual. The text could explicitly discuss developmental issues that permeate the assessment of irritability and the diagnosis of mood disorders as well as the difficulties faced in diagnosing bipolar disorder in children. The requirement of distinct mood episodes could be highlighted. The diagnostic criteria for manic, mixed, and hypomanic episodes could include specific warnings to exercise substantial caution in making these diagnoses when the presentation consisted of irritable mood only with nonspecific symptoms of mania such as motor hyperactivity, rapid speech, and distractibility. Additional specifications and subcategories within the bipolar disorder not otherwise specified diagnosis would facilitate ongoing research and will be clinically useful. These changes would improve diagnostic classification in adults as well. Finally, there could be specific warnings to exercise extreme caution in making a diagnosis of bipolar disorder in children under the age of 6 years. Nevertheless, we cannot expect that a substantial proportion of the diagnostic controversies and difficulties surrounding the diagnosis of bipolar disorder in youth can be solved by the *DSM-5*.

In summary, we strongly disagree with the inclusion of TDD as a new formal diagnosis in the *DSM-5*. The level of scientific evidence to support TDD is too limited to justify a new diagnostic entity. Application of the TDD criteria in clinical practice would most likely label a highly heterogeneous group of children and adolescents who will have divergent developmental trajectories of psychopathology. Temper dysregulation disorder with dysphoria is unlikely to be a treatment-relevant phenotype, and subsets of youths meeting TDD criteria might optimally respond to completely different types of pharmacologic and psychosocial interventions. In addition, including the TDD diagnosis in the *DSM-5* would likely spur the pharmaceutical industry to seek FDA approval for TDD as an indication, resulting in the substantial expansion of use of medications for youths with irritability. For some youths, this could be beneficial; however, for the potentially large subset that would respond well to psychosocial interventions, it could mean unnecessary exposure to psychotropic medication. As youths with a broad range of symptomatology are lumped together into the TDD diagnostic category, research into the pathophysiology and treatment of youths with severe irritability would be adversely affected—greater heterogeneity would reduce the signal to noise ratio. Inclusion of TDD would compromise the already precarious public perception of child and adolescent psychiatry. There are better ways to address the diagnostic difficulties associated with bipolar disorder in youth than creating a new, unsubstantiated diagnosis such as TDD.

Author affiliations: Department of Psychiatry, University of Pittsburgh School of Medicine—Western Psychiatric Institute and Clinic, Pennsylvania (Drs Axelson, Birmaher, T. Goldstein, Ryan, and Diler); Department of Psychiatry, Division of Child and Adolescent Psychiatry, Case Western Reserve University, Cleveland, Ohio (Dr Findling); Department of Psychiatry, Division of Child and Adolescent Psychiatry, Ohio State University, Columbus (Drs Fristad and Arnold); Division of Psychiatry, Cincinnati Children's Hospital Medical Center, Ohio (Dr Kowatch); Department of Psychology, University of North Carolina at Chapel Hill (Dr Youngstrom); Department of Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (Dr B.Goldstein); Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California (Dr Chang); Department of Psychiatry, University of Cincinnati, College of Medicine, Ohio (Dr DelBello).

Potential conflicts of interest: **Dr Arnold** has had research support from Shire, Lilly, Curemark, and Neuropharm, honoraria from Abbott, Organon, Targacept, Novartis, McNeil, and Shire, and has served on speakers or advisory boards for Shire, McNeil, Targacept, and Novartis. **Dr Birmaher** is a consultant for Schering Plough and receives royalties for publications from Random House, Inc, and Lippincott Williams & Wilkins. **Dr Chang** is a consultant for Bristol-Myers Squibb, has received research support from Glaxo Smith Kline, and served as a speaker for Merck. **Dr DelBello** has received research support from AstraZeneca, Eli Lilly, Johnson and Johnson, Shire, Janssen, Pfizer, Bristol Myers Squibb, Repligen, Martek, Somerset, GlaxoSmithKline, and Sumitomo; has served on lecture bureaus for Bristol-Myers Squibb, and Schering Plough; and has consulted for and/or served on an advisory board for GlaxoSmithKline, Eli Lilly, Pfizer, and Schering Plough. **Dr Findling** receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Abbott, Addrenex, AstraZeneca, Biovail, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, KemPharm Lilly, Lundbeck, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, sanofi-aventis, Schering-Plough, Sepracore, Shire, Solvay, Supernus Pharmaceuticals, Validus, and Wyeth. **Dr B. Goldstein** has received honoraria from Purdue Pharma and research support from Pfizer. **Dr Kowatch** has served as a consultant for Forest, AstraZeneca, Merck, Medscape, and Physicians Postgraduate Press, Inc, and has served on a speaker's bureau for AstraZeneca. **Drs Axelson**, **Fristad**, **Youngstrom**, **T. Goldstein**, **Ryan**, and **Diler** do not have any potential conflicts of interest to disclose. All authors are investigators in research projects that focus on the phenomenology, neurobiology, and/or treatment of youths with bipolar disorder.

Funding/support: Faculty effort associated with production of this article was supported in part by the following grants from the National Institute of Mental Health: R01 MH073953; R01 MH073801; R01 MH073816; R01 MH073967; and from the Sunnybrook Foundation.

REFERENCES

1. Leibenluft E, Charney DS, Towbin KE, et al. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry*. 2003;160(3):430–437.
2. Issues Pertinent to a Developmental Approach to Bipolar Disorder in *DSM-5*. 2010. http://www.dsm5.org/Proposed%20Revision%20Attachments/APA%20Developmental%20Approaches%20to%20Bipolar%20Disorder.pdf. Accessed February 27, 2010.
3. DSM-5 Childhood and Adolescent Disorders Work Group. Justification for Temper Dysregulation Disorder With Dysphoria. Washington, DC: American Psychiatric Association; 2010. http://www.dsm5.org/Proposed%20Revision%20Attachments/Justification%20for%20Temper%20Dysregulation%20Disorder%20with%20Dysphoria.pdf. Accessed March 3, 2011.
4. Dickstein DP, Rich BA, Binstock AB, et al. Comorbid anxiety in phenotypes of pediatric bipolar disorder. *J Child Adolesc Psychopharmacol*. 2005;15(4):534–548.
5. Guyer AE, McClure EB, Adler AD, et al. Specificity of facial expression labeling deficits in childhood psychopathology. *J Child Psychol Psychiatry*. 2007;48(9):863–871.
6. Brotman MA, Schmajuk M, Rich BA, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biol Psychiatry*. 2006;60(9):991–997.
7. Carey B. Revising Book On Disorders Of the Mind. *New York Times*. 2010 February 10. http://www.nytimes.com/2010/02/10/health/10psych.html. Accessed March 8, 2011.

© Copyright 2011 Physicians Postgraduate Press, Inc. © Copyright 2011 Physicians Postgraduate Press, Inc.

8. Spiegel A. Children labeled 'bipolar' may get a new diagnosis [transcript]. *All Things Considered*. National Public Radio; February 10, 2010. http://www.npr.org/templates/story/story.php?storyId=123544191. Accessed March 7, 2011.
9. Will G. Handbook suggests that deviations from 'normality' are disorders. *Washington Post*. February 28, 2010. http://www.washingtonpost.com/wp-dyn/content/article/2010/02/26/AR2010022603369.html. Accessed March 7, 2011.
10. Campbell M, Adams PB, Small AM, et al. Lithium in hospitalized aggressive children with conduct disorder: a double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 1995;34(4):445–453.
11. Campbell M, Small AM, Green WH, et al. Behavioral efficacy of haloperidol and lithium carbonate: a comparison in hospitalized aggressive children with conduct disorder. *Arch Gen Psychiatry*. 1984;41(7):650–656.
12. Malone RP, Delaney MA, Luebbert JF, et al. A double-blind placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. *Arch Gen Psychiatry*. 2000;57(7):649–654.
13. Findling RL, McNamara NK, Branicky LA, et al. A double-blind pilot study of risperidone in the treatment of conduct disorder. *J Am Acad Child Adolesc Psychiatry*. 2000;39(4):509–516.
14. Steiner H, Petersen ML, Saxena K, et al. Divalproex sodium for the treatment of conduct disorder: a randomized controlled clinical trial. *J Clin Psychiatry*. 2003;64(10):1183–1191.
15. Moreno C, Laje G, Blanco C, et al. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry*. 2007;64(9):1032–1039.
16. Kessler RC, Avenevoli S, Green J, et al. National comorbidity survey replication adolescent supplement (NCS-A): III. Concordance of DSM-IV/CIDI diagnoses with clinical reassessments. *J Am Acad Child Adolesc Psychiatry*. 2009;48(4):386–399.
17. Copeland WE, Shanahan L, Costello EJ, et al. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch Gen Psychiatry*. 2009;66(7):764–772.
18. Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: irritable, headstrong, and hurtful behaviors have distinctive predictions. *J Am Acad Child Adolesc Psychiatry*. 2009;48(4):404–412.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

© Copyright 2011 Physicians Postgraduate Press, Inc. © Copyright 2011 Physicians Postgraduate Press, Inc.

Mary Ann Liebert, Inc., 140 Huguenot Street, New Rochelle, NY 10801