Justification for Temper Dysregulation Disorder with Dysphoria

DSM-5 Childhood and Adolescent Disorders Work Group

Proposed change:

Introduction of a diagnostic category for temper dysregulation with dysphoria (TDD) into the Mood Disorders Section of DSM-V

I. Explication of the reason for a proposed change

A. Background

One of the most dramatic developments in child psychiatry in the past decade has been a marked upsurge in the rate at which children are being assigned the diagnosis of bipolar disorder (BD) (Moreno et al, 2007; Blader and Carlson, 2007). Moreno et al (2007) found a 40-fold increase between 1994 and 2003 in the number of outpatient pediatric psychiatry visits associated with the diagnosis of BD, while Blader and Carlson (2007) found that the rate of hospital discharges in the U.S. of youth with a primary diagnosis of BD increased from 1.3 to 7.3 per 10,000 between 1996 and 2004. This increase could be seen as reflecting appropriate diagnosis coming after a time of persistent under-diagnosis. However, this increase coincided with a time period during which some child psychiatry researchers and practitioners adopted new conventions in assigning the diagnosis of BD to children. These conventions would be expected to broaden the phenotype of pediatric BD, beyond the explicit boundaries of DSM-IV BD. The DSM-IV conventions, and those of all previous editions of the DSM, are based primarily in work on adults.

Beginning with the DSM-IV revision, a major focus in the DSM process has been to maintain continuity between adult and child conventions as much as possible. With this focus, developmental modifications to nosology are only viewed as justified when they are supported strongly by data on validity. This heavily shaped revisions of DSM-III-R to create DSM-IV, and the Child Disorders Work Group recognized the importance of this approach in revising DSM-IV to create DSM-V. In the case of BD, the Childhood Disorders Work Group spent considerable time reviewing the relevant research literature on pediatric BD. The Work Group's deliberations focused on integrating a critical review of the research literature with the considerable clinical experience of its members, in order to determine the most appropriate developmental modifications to the BD diagnosis.

In its deliberations, the Childhood Disorders Work Group was keenly aware that research demonstrates that the "classic" adult phenotype clearly does present in pre-pubertal children, as well as in adolescents, although it may be rare in the younger age group. Unambiguous agreement about this fact weighed heavily in the Work Group's deliberations. The agreement on the existence of this classic phenotype generates an important standard against which all other phenotypes can be compared in terms of longitudinal course, family history, and pathophysiology. Thus, deliberations heavily weighed research comparing alternative BD phenotypes against classic BD, in terms of external validators recognized in the DSM-V Task Force Guidelines. Among these validators, the Childhood Disorders Workgroup followed the Guidelines in

considering longitudinal outcome to be particularly important. This approach also reflected the salience of longitudinal research for drawing conclusions about development, combined with the lack of well-validated biomarkers for BD in any age group, and the absence of data on differential treatment response or genetics in classic as opposed to alternative pediatric BD phenotypes. Therefore, more than any other consideration, the Work Group noted that a putative, alternative childhood BD phenotype that differed in its symptom patterns from classic BD would be expected to have longitudinal continuity with the classic DSM-IV BD phenotype.

In devising a developmental strategy for BD in DSM-V, the Childhood Disorders Work Group worked closely with the Mood Disorders Work Group. The integrated strategy devised by the two groups is outlined in "Issues Pertinent to a Developmental Approach to Bipolar Disorder in DSM-V," posted under the Mood Disorders Work Group. In devising the strategy, the Work Groups targeted three particularly salient issues: 1) a lack of clarity in the DSM-IV as to how researchers and clinicians should operationalize episodicity in the context of a manic or hypomanic episode; 2) the question of whether severe, non-episodic irritability is a developmental presentation of mania; and 3) the nosological status of hypomanic episodes shorter than four days.

In this document, we will describe in detail the Work Groups' approach to # 2 above i.e., the question of whether severe, non-episodic irritability is a developmental presentation of mania. It should be noted that attempts to answer this question follow closely the guidelines for change, laid forth by the DSM-V Task Force. Importantly, these guidelines involve two sets of considerations: one related to a scientific evaluation of the evidence and another related to clinical concerns. The current document focuses in most depth on a critical evaluation of the scientific evidence. The accompanying document, "Issues Pertinent to a Developmental Approach to Bipolar Disorder in DSM-V," posted under the Mood Disorders Work Group, focuses less deeply on the scientific evidence and more closely on weighing both scientific evidence and clinical need; a summary of those considerations is also included in this document, section III. The careful weighing of both scientific and clinical factors led to the decision to propose a new diagnosis.

The Work Groups' new diagnosis adopts a new name not used previously in the psychiatric literature, Temper Dysregulation Disorder with Dysphoria. The Work Group proposes that this diagnosis be added to DSM-V, and the basis for that proposal is elucidated in this document. For more information about the Work Groups' approach to addressing the lack of clarity in operationalizing a (hypo)manic episode (#1 above), or to the nosological status of hypomanic episodes shorter than four days (# 3, above), please see in "Issues Pertinent to a Developmental Approach to Bipolar Disorder in DSM-V," posted under the Mood Disorders Work Group.

B. Rationale for introducing a diagnostic category for temper dysregulation with dysphoria (TDD) within the mood disorders section of DSM-V

As noted above, within the last decade a school of thought has developed amongst some researchers and clinicians that severe, non-episodic irritability is characteristic of pediatric BD. That is, the contention has been that mania manifests in youth, not episodically as in DSM-IV, but instead as severe, non-episodic irritability (Biederman et al, 2004; Mick et al, 2005). Given the upsurge in the rate of the diagnosis of pediatric BD, and the question as to whether severe, non-episodic irritability should be viewed as a developmental phenotype of pediatric BD, research over the past 8 years has compared youth with such irritability to those with episodic DSM-IV BD. To facilitate this research, a syndrome called severe mood dysregulation (SMD) was defined. The criteria for SMD require severe, non-episodic irritability and anger outbursts, as well as symptoms of hyperarousal (specifically, those symptoms of attention deficit hyperactivity disorder (ADHD) that overlap with the "B" criteria of mania) (Leibenluft et al, 2003). As detailed below, research indicates that youth with SMD differ from those with DSM-IV BD in outcome, gender distribution, and possibly family history and pathophysiology. In considering the possible adoption of an SMD-like phenotype to DSM-V, the Childhood Disorders Work Group decided to rename the syndrome temper dysregulation with dysphoria (TDD) because a) the new name is more descriptive; and b) the name of DSM diagnoses does not typically include a denotation of severity. In addition, the Work Group decided to eliminate the hyper-arousal criteria, since the consensus was that these symptoms could be indicated by assigning to the child an additional diagnosis of ADHD. The research discussed in this document was conducted using the inclusion criteria for SMD but, given the relatively minimal differences between those and the proposed criteria for TDD, data regarding SMD is informative with respect to TDD.

Importantly, youth with SMD are as severely impaired as those with BD. For example, investigators at the NIMH-IRP recruited 111 BD and 118 SMD (mean age BD: 12.9 $\pm$ 2.8, SMD: 11.6 $\pm$ 2.5) from around the country. In these samples, the mean Children's Global Assessment Scale rating was 51.1 $\pm$ 10.8 for BD and 47.4 $\pm$ 9.0 for SMD, suggesting that these two syndromes can present with similar levels of severity. Number of medications and percent with a lifetime history of psychiatric hospitalization also was similar between the two patient groups, further supporting this suggestion. In DSM-IV terms, approximately 85% of SMD youth meet criteria for ADHD and oppositional defiant disorder (ODD), but these diagnoses communicate neither the significant impairment of SMD youth nor the severe mood disorder from which they suffer. Indeed, it is plausible that clinicians assign the diagnosis of BD to SMD youth in part because the BD diagnosis justifies access to a higher level of resources. Furthermore, children with severe irritability frequently meet DSM criteria for an anxiety disorder, and many have a history of major depression; of course, the fact that these children meet criteria for other disorders (specifically, disruptive behavior disorders) further complicates their classification. The current

convention, which involves categorizing them as BD, clearly creates clinical problems. This renders treatment with antidepressants or stimulants relatively contraindicated without concurrent mood stabilizers or antipsychotics. Therefore, the treatment implications of differentiating this subtype are considerable.

It can certainly be argued that it is premature to suggest the addition of the TDD diagnosis to DSM-V, since the work has been done predominately by one research group in a select research setting, and many questions remain unanswered. Indeed, a subgroup of the ADHD and Disruptive Behavior Disorders and Childhood Disorder Work Groups expended considerable energy devising a proposal for a specifier for the Oppositional Defiant Disorder (ODD) diagnosis that would differentiate the SMD/TDD phenotype from the rest of ODD, given that new specifiers require a lower level of evidence than do new diagnoses. However, at the March, 2009 meeting, the two work groups decided that an ODD specifier would be unlikely to be used by clinicians to diagnose youth with SMD/TDD, since ODD is not a mood disorder (while TDD would be). Furthermore, given the wide degree of impairment amongst youth with ODD, patients assigned that diagnosis may not be given access to the intense level of services required by SMD/TDD youth. Moreover, the SMD/TDD phenotype appears to be quite common in the community. For example, one large (N=1420), prospective epidemiological study generated proxy diagnoses for SMD, using answers to questions from structured psychiatric interviews. In this study, the lifetime prevalence of the proxy SMD diagnosis in youth ages 10.6 $\pm$ 1.4y old to 18.3 $\pm$ 2.1 y old was 3.2% (Brotman et al, 2006). Hence, syndromes highly similar to SMD, such as TDD, are likely to be common, both in the clinic but also in the community. Given this high prevalence of the SMD/TDD phenotype, and the severity of its symptomatology, it is important for these severely impaired youth to have a "home" in the DSM, so that clinicians can provide the intensive care that they require. In addition, having a separate diagnosis for TDD will foster further research on this common and severe mood disorder.

II. Evidence for change: Validators

A. Tier 1:

1. Outcome

A crucial question is whether youth with SMD/TDD develop episodic DSM-IV BD as they age. If so, that would be a powerful argument for changing the DSM-IV criteria for mania to include non-episodic irritability. On the other hand, if youth with SMD/TDD do not develop BD in adulthood, then such youth should not be diagnosed with BD, and must fit into another DSM category.

Two published studies use existing longitudinal community-based data sets to address the question of whether SMD, or irritability in youth, predicts BD in adulthood. In the first of these

(Brotman et al, 2006), a post-hoc analysis of the Great Smoky Mountain (GSMS) data set (N=1420) compared youth who met criteria for SMD at age 10.6 ± 1.4 to those who did not in terms of outcome at age 18.3 ± 2.1 (since this was a post-hoc analysis, the criteria used were slightly modified from those used in clinical studies of SMD). At the follow-up point, the two groups differed only in their risk for unipolar depressive disorders, which was elevated in those with SMD at the earlier time point. The GSMS includes very few cases of BD, the follow-up point is not beyond the age of risk for BD, and the identification of SMD was done post-hoc; because of the modifications in criteria, the SMD sample in this study, may include children who are not as severely impaired as are those in our clinical sample. Nonetheless, these data provide preliminary evidence that SMD predicts unipolar depressive disorders, not BD, in early adulthood.

A similar conclusion was reached in post-hoc analyses of the Children in the Community study (N=776) (Leibenluft et al, 2006; Stringaris et al, 2009). The assessment of subjects in this study did not allow for the identification of youth with SMD, but did allow for the differentiation of chronic from episodic irritability. Data indicated that chronic irritability present at age 13.8 predicated increased risk for major depression, generalized anxiety disorder, and dysthymia at age 33.2. Importantly, this study follows subjects through the bulk of the age of risk for BD, and has enough subjects meeting criteria for BD to detect an association with adolescent chronic irritability. These data in SMD and chronic irritability are consistent with studies indicating that oppositional defiant disorder (ODD) is a risk factor for depression and anxiety, but not BD (e.g., Burke et al, 2005; Copeland et al., 2009).

Importantly, these longitudinal studies are open to criticism, since the subjects in were drawn from the community, and few were treated in mental health clinics, a setting highly important for DSM-V. Moreover, since these studies used proxy definitions of SMD, it remains unclear the degree to which longitudinal course in these studies is similar to that in patients with SMD/TDD seen in clinics. Important, relevant data emerges from a longitudinal study performed in the clinical sample recruited at the NIMH. This study, like the two above-noted epidemiologically-based studies, suggests that youth with SMD do not, over time, develop manic episodes (Stringaris et al, in revision). Only one out 84 subjects with SMD [1/84 (1.20%); 95% CI 0.0003 to 0.064] experienced a (hypo-)manic or mixed episode during the study (median follow up=28.4 months); these data contrast with data collected using identical procedures in the other sample of children studied at NIMH, those with the “classic” presentation of BD. In the sample of youth with narrowly-defined BD, the frequency of (hypo-)manic or mixed episodes was 50 times higher than in those with SMD [58/93 BD (62.4%);95% CI 0.52 to 0.72]; the difference between the groups was significant ($z=-8.61$; $p<0.00001$). Thus, preliminary data suggest that children with SMD seen in the clinic do not manifest manic episodes when they are followed longitudinally. Moreover, the failure to detect such manic episodes in this study cannot be attributed to insensitivity of the methods used, since these same methods generate expectable rates of manic

episodes in a comparably ill sample with BD, assessed using identical procedures. Limitations of this study include the relatively small sample and short follow-up, as well as ascertainment bias. However, that bias would presumably mean that subjects recruited at the NIMH are particularly severely impaired, and yet only one out of 84 SMD subjects developed a (hypo)manic episode. Moreover, the most relevant findings, concerning the course of SMD evaluated in the clinic, confirm the findings from the epidemiological studies that do not have these same limitations.

In sum, longitudinal studies suggest that youth with SMD or non-episodic irritability are at increased risk for unipolar depressive and anxiety disorders in adulthood, but not BD. To the extent that youth with TDD should have a "home" in DSM-V, these longitudinal data suggest that that home should not be in the BD category.

2. Familial aggregation and/or co-aggregation (i.e., family, twin or adoption studies)

The data here are limited but again suggest that the SMD/TDD phenotype should be differentiated from BD. In a pilot study, parents of youth with BD were significantly more likely to themselves have BD than were parents of youth with SMD. The two groups of parents did not differ in rates of anxiety disorders, unipolar depressive disorders, or substance abuse. The study is small and subject to ascertainment bias (Brotman et al, 2007).

B. Tier 2: Biological markers

As with all biological markers in psychiatry, data here must be regarded as very preliminary. Although both youth with BD and those with SMD have deficits in face emotion labeling, the neural circuitry mediating these deficits appears to differ between groups (Brotman et al, 2010; Guyer et al, 2007; Rich et al, 2008). Of note, in Brotman et al, 2010, amygdala activity differed, not only between SMD and BD, but also between SMD and ADHD. Similarly, when performing a frustrating task, both youth with BD and those with SMD express more frustration than do controls. However, the neural circuitry mediating this emotional reactivity differ between groups, with BD patients showing deficient executive attention in parietal regions, while SMD youth show deficits in early attentional processes (Rich et al, 2007). Finally, both SMD and BD youth show deficits on response reversal and cognitive flexibility tasks, but those deficits are more consistent and widespread in BD than in SMD (Dickstein et al, 2007). Therefore, preliminary research on biomarkers suggests differences in brain function between SMD and BD.

C. Tier 3: Socio-demographic factors such as sex, age at onset and social class distribution

Considerable data indicate that rates of bipolar I disorder in adults do not differ by gender. Similarly, there appears to be an even gender distribution of episodic BD I disorder in youth (Birmaher et al., 2009). However, in the study documenting the increase in the number of

outpatient visits associated with pediatric BD, the patients diagnosed with BD were disproportionately male (66.5%) (Moreno et al, 2007). Similarly, SMD appears to be more common in boys than in girls (77.6% in an epidemiologic sample (Brotman et al., 2006) and 66.7% in a clinical sample (Stringaris et al, in revision). Again, this suggests that SMD may be a distinct syndrome from BD.

III. Additional considerations:

A. A need for the category

As described above, the current upsurge in the rates of diagnosis of pediatric BD, as well as an epidemiologic study (Brotman et al, 2006) suggests that the syndrome of severe, non-episodic irritability is common in children; that these children are severely impaired psychiatrically; and that they do not fit well into any existing DSM category. The question of whether youth with the SMD/TDD phenotype have a form of BD, vs. a syndrome on a pathophysiological continuum with anxiety disorders, unipolar depression, and ADHD, has profound treatment implications. That is, if TDD is a form of BD, first-line treatment would consist of atypical antipsychotic medication and/or mood stabilizers. On the other hand, if TDD is on a continuum with unipolar depressive disorders, anxiety disorders, and ADHD, first-line treatment would consist of serotonergic reuptake inhibitor antidepressants (SSRI's) and stimulants. Importantly, the latter two medication classes are considered relatively contraindicated in BD. Thus, nosological questions regarding TDD have significant treatment implications, and it is essential that clinical trials to address this question be launched (see also III.D, below).

B. Relationship with Other DSM-V Disorders

As outlined in this document, the data differentiating the TDD/SMD phenotype from BD in terms of longitudinal outcome is reasonably strong, and the family history, demographic, and pathophysiologic data are suggestive. On the other hand, TDD/SMD cannot be differentiated from ODD. Indeed, the TDD phenotype can be conceptualized as the most severely irritable of patients with ODD. Data analyses performed by the Childhood Disorders Work Group suggest that approximately 15% of patients with ODD would meet criteria for TDD, and by definition almost all youth meeting criteria for TDD would also meet criteria for ODD. For this reason, as noted above, the Work Group began with the assumption that we would propose a specifier to ODD, rather than proposing a separate diagnosis for TDD. However, while the scientific data may suggest defining TDD as a specifier to ODD, the Task Force Guidelines note the appropriateness of also weighing clinical considerations in the decision as to whether to propose a new diagnosis, and

the Work Group ultimately concluded that a specifier would not meet the clinical needs of children with TDD.

Specifically, the Childhood and Disruptive Behavior Disorder Work Groups noted that Task Force Guidelines specify that new disorders could be proposed in order to identify a distinct group of people who need considerable clinical attention, where there is currently a lack of public awareness of this need. In addition, the Guidelines specify that a new disorder could be justified to focus attention on the need to generate effective biological, psychological, and social treatments for a neglected, but important, clinical syndrome. For the following reasons, the Work Groups decided that proposing TDD as a new diagnosis would be consistent with these Task Force Guidelines. ODD is categorized as a disruptive behavior disorder, while TDD would be categorized as a mood disorder. It is important to provide a mood disorder diagnosis for youth with TDD in order to focus clinicians' attention on these youths' significantly impairing mood symptoms. In addition, TDD youth require considerably more services than do the significant majority of youth with ODD. For example, in the NIMH sample (N=118, mean age 11.6 $\pm$ 2.5), 35% of the sample had a history of at least one psychiatric hospitalization and, as noted above, standardized measures of impairment show no difference between youth with SMD and those with BD. In addition, youth with SMD/TDD typically receive treatment with mood stabilizers and/or antipsychotics, in addition to SSRI's and stimulants. Arguably, this is one reason why so many TDD youth are receiving the diagnosis of BD. Clinical trials targeted toward the TDD population are sorely needed, in order to begin to address the neglected clinical needs of these very severely impaired patients. Thus, when considering the potential clinical benefit and harm of the two alternative approaches (new diagnosis vs. ODD specifier), the balance was thought to favor strongly the inclusion of TDD as a newly-defined syndrome in the Mood Disorders section. For further discussion on this point, please see "Issues Pertinent to a Developmental Approach to Bipolar Disorder in DSM-V," posted under the Mood Disorders Work Group.

C. Potential Harm

Two potential harms should be considered: those associated with adding TDD as a diagnosis in DSM-V, and those associated with not making such a change. With regard to not adding TDD as a diagnosis, the potential harm is that the diagnosis of BD will continue to be assigned to a substantial number of youth who do not actually meet criteria for the illness. This stands as a current major problem in the field; failing to provide clinicians with a more appropriate category in which to place these children runs the risk of not addressing this major problem. Offering such an alternative, such as TDD, might address this problem, and failing to do so would allow it to continue (see explication, p. 1). As noted above, the fact that many youth with the TDD phenotype are receiving the diagnosis of BD, which may result in suboptimal treatment.

The harm associated with the change is the risk that the diagnosis of TDD will become prematurely reified, given that there is relatively little research on this population of children, and the research has emanated from one research group. Establishing the diagnosis of TDD will not only provide a "home" for these severely impaired youth, but will also "jump-start" research on severe irritability in youth. Severe irritability is a very prevalent mood symptom that has received relatively little research attention; arguably, this lack of research attention has been a major contributor to the current controversy as to how children who present with severe irritability as a chief complaint should be diagnosed and treated. As research data are gathered, and as the dimensional approach to psychiatric diagnosis matures, it would be important for there to be flexibility about modifications to the TDD criteria in future editions of DSM.

D. Available Treatments

The only treatment trial of SMD used lithium and did not show efficacy vs. placebo (Dickstein et al, 2009). One of the major advantages of having a diagnostic category for SMD would be to foster more research on treatment for these very severely impaired children. At this time, little research is being conducted, in part because they do not fit into a defined DSM category.

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Draft Criteria for Temper Dysregulation Disorder with Dysphoria

A. The disorder is characterized by severe recurrent *temper outbursts* in response to common stressors.

1. The temper outbursts are manifest verbally and/or behaviorally, such as in the form of verbal rages, or physical aggression towards people or property.
2. The reaction is grossly out of proportion in intensity or duration to the situation or provocation.
3. The responses are inconsistent with developmental level.

B. *Frequency*: The temper outbursts occur, on average, three or more times per week.

C. *Mood between temper outbursts:*

1. Nearly every day, the mood between temper outbursts is persistently negative (irritable, angry, and/or sad).
2. The negative mood is observable by others (e.g., parents, teachers, peers).

D. *Duration*: Criteria A-C have been present for at least 12 months. Throughout that time, the person has never been without the symptoms of Criteria A-C for more than 3 months at a time.

E. The temper outbursts and/or negative mood are present in at least two settings (at home, at school, or with peers) and must be severe in at least in one setting.

F. Chronological age is at least 6 years (or equivalent developmental level).

G. The onset is before age 10 years.

H. In the past year, there has never been a distinct period lasting more than one day during which abnormally elevated or expansive mood was present most of the day for most days, and the abnormally elevated or expansive mood was accompanied by the onset, or worsening, of three of the "B" criteria of mania (i.e., grandiosity or inflated self esteem, decreased need for sleep, pressured speech, flight of ideas, distractibility, increase in goal directed activity, or excessive involvement in activities with a high potential for painful consequences; see pp. XX). Abnormally elevated mood should be differentiated from developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation.

I. The behaviors do not occur exclusively during the course of a Psychotic or Mood Disorder (e.g., Major Depressive Disorder, Dysthymic Disorder, Bipolar Disorder) and are not better accounted for by another mental disorder (e.g., Pervasive Developmental Disorder, post-traumatic stress disorder, separation anxiety disorder). (Note: This diagnosis can co-exist with Oppositional Defiant Disorder, ADHD, Conduct Disorder, and Substance Use Disorders.) The symptoms are not due to the direct physiological effects of a drug of abuse, or to a general medical or neurological condition.