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Beyond Dogma: From Diagnostic Controversies to Data About Pediatric Bipolar Disorder and Children with Chronic Irritability and Mood Dysregulation

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Abstract

From the mid-1990s through the present, studies have demonstrated a significant rise in the numbers of children and adolescents diagnosed with bipolar disorder (BD). Why is this? The present manuscript reviews several possibilities, most notably ambiguity in the diagnostic criteria for mania and how they may apply to children with functionally-impairing irritability. Furthermore, we discuss ongoing phenomenological and affective neuroscience research approaches to address those children most on the fringes of our current psychiatric nosology. In summary, these studies suggest that BD youths may be distinguished on some measures from those with chronic irritability and severe mood dysregulation, although the two groups also have some shared deficits.

INTRODUCTION

Pediatric bipolar disorder (BD) continues to be among the most controversial of all psychiatric disorders affecting children and adolescents today. In particular, while pediatric BD was once thought to be exceedingly rare, recent studies demonstrate a marked increase in numbers of children and adolescents receiving the diagnosis of BD. For example, the percentage of children and adolescents discharged from psychiatric hospitals in the U.S. with a diagnosis of BD has surged from less than 10% in the mid- 1990s to more than 20% in the mid-2000s (1). This rise is not only an inpatient phenomenon as another study demonstrated a forty-fold rise in the incidence of outpatient visits assigned the diagnosis of BD during a similar period, from 25/100,000 in 1993-1994 to 1003/100,000 in 2002-2003 (2). Moreover, this increase is not just occurring in the U.S., but in other countries as well. For example, rates of under 19 year olds admitted to German psychiatric hospitals increased 68.5% from 1.13/100,000 in 2000 to 1.91/100,000 in 2007, an increase which exceeded the general trend for mental health disorder admissions (3). It remains unclear if these trends represent increased awareness of a serious problem (akin to recognition of the prevalence

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and impact of childhood depression in the 1980s), a non-specific rise in children and adolescents diagnosed with psychopathology (1), or misdiagnosis.

The purpose of the manuscript is to explore the controversy surrounding pediatric BD by: (a) discussing factors related to why more children are being diagnosed with BD, including new interpretations of diagnostic criteria; (b) reviewing research approaches to advance our phenomenological and biological understanding of irritability in children; (c) presenting potential noslogical changes in DSM-V related to these research findings that will likely impact how BD is diagnosed, especially in children and adolescents.

FACTORS RELATED TO THE RISE OF PEDIATRIC BD

The controversy about pediatric BD centers not just on the observation that more children are being diagnosed with BD, but also on the question of why? While we really do not know the cause for this rise, and likely have no way of knowing definitively, there are several possible explanations.

One factor that may have contributed to the increased rates in the diagnosis of BD in children is ambiguity in the DSM-IV criteria for a manic episode. According to DSM-IV, a manic episode consists of ("A" criterion) "a distinct period of abnormally and persistently elevated, expansive or irritable mood," lasting at least 1 week (or any duration if hospitalization is necessary). This period must be accompanied by at least three of the following "B" symptoms (at least four if the mood was only irritable): 1. inflated self-esteem or grandiosity, 2. decreased need for sleep (e.g., feels rested after only 3 hours of sleep), 3. more talkative than usual or pressure to keep talking, 4. flight of ideas or subjective experience that thoughts are racing, 5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), 6. increase in goal-directed activity (at work, at school, or sexually) or psychomotor agitation, or 7. excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees or sexual indiscretions). Three aspects of these criteria make establishing the diagnosis of BD difficult, especially in children: (a) duration of a manic episode, (b) irritability vs. euphoria in defining a manic episode, and (c) overlap with other illnesses, including attention deficit hyperactivity disorder (ADHD).

First, with respect to the DSM-IV criterion specifying the minimum duration of a manic episode, the key problem is insufficient detail about the temporal characteristics of the manic symptoms. Notably, these characteristics are much more poorly specified for manic than for depressive episodes. Specifically, the DSM-IV "A" criteria for a major depressive episode requires that the depressive symptoms last "most of the day, nearly every day." In contrast, the "A" criterion for a manic episode requires only "a distinct period" lasting 1 week. How much of that week (or more) must the mood change persist? Should it be most of the day every day, or parts of days? If parts of days, then how do we determine if a child with several irritable periods in a single week, with resultant impairment, is having a manic episode, or instead a series of temper tantrums that might be part of typical development? What is the shortest duration of these symptoms that would be considered a manic episode versus a developmentally appropriate mood fluctuation? This nosological inconsistency has

led to divergent views about the course of BD, most prominently – but not exclusively – expressed by those studying children, with some adhering to the classical view that pediatric BD is an episodic illness, with sustained periods (days to weeks) of mania, depression, and euthymia (normal mood) (4, 5), while others maintain that pediatric BD is a chronic illness, with fluctuations between all three mood states occurring as rapidly as within a single day (known by some as “ultradian cycling”) (6-11). Both views are held by clinicians working with adults and children with BD, although it is possible such non-DSM terms, including ultradian cycling, have created more confusion rather than less. In a related manner, data from the BRIDGE study (Bipolar Disorders: Improving Diagnosis, Guidance, and Education) suggest that it may be more appropriate to define manic episodes on a continuum, rather than categorically defining who does and who does not have BD. Specifically, they found that 47% (2,647/5,635) of adults with unipolar major depression episode met criteria for the bipolar specifier (i.e., short-lived manic episodes with full “B” symptoms), with similar rates of external validators of BD, such as family history of mania/hypomania and multiple prior mood episodes (11). However, it should be noted that the BRIDGE study's findings are somewhat limited due to lack of reliability among clinician raters and the lack of direct interviews of family members to validate patient reports of family history. Nevertheless, the temporal duration and fluctuation of mania is very much the subject of ongoing research in both children and adults.

The definition of an episode is also germane to the common problem of sorting out what is a temper tantrum, or anger outburst, and what is irritable mania. One possible solution is reaffirming the DSM requirement that a manic episode requires the combination of mood change (elevated, expansive, or irritable) plus sufficient “B” symptoms and resultant functional impairment, rather than just mood symptoms or just “B” symptoms alone. However, this is only a partial solution given the abovementioned issues related to the duration of the mood-defining symptoms that allow for interpretation, rather than providing a clear-cut rule.

The second aspect of the DSM-IV mania criteria that often leads to confusion is whether the “abnormally and persistently” altered mood is elevated/expansive (known commonly as “euphoria”) or irritable. Although euphoric mood is uniquely part of mania, the presence of euphoria is not necessary to diagnose BD because irritable mood can also qualify for a manic episode. These are differentially weighted in DSM-IV, so that the patient must have three associated “B” symptoms if the mood is primarily euphoric, and four if the mood is primarily irritable, to qualify for a manic episode. Moreover, irritability is not specific to mania. Instead, it is an explicit diagnostic criterion for several DSM-IV disorders, such as generalized anxiety disorder, post-traumatic stress disorder, and child-specific modified criteria for a major depressive episode. In addition, irritability is implied by criteria for oppositional defiant disorder (ODD), although the word irritability is not used explicitly. Furthermore, irritability is an associated symptom in pervasive developmental delay spectrum disorders (autism, Asperger's) and ADHD (12). Further complicating matters is the fact that DSM-IV does not provide (a) a clear definition of irritability for any of these disorders, (b) developmentally informed examples of how these symptoms differ among these disorders – i.e., in children, adolescents, young adults, and adults; or (c) examples of how irritability associated with mania is different from that present in typical-development –

i.e., a temper tantrum. Thus, the same functionally-impairing irritability might be called mania by some clinicians and not by others, depending on how they interpret the “A” and “B” criteria for mania. One final factor adding to the confusion is the fact that some have suggested that euphoria is not necessary for establishing a diagnosis of BD (13).

The third DSM-IV related factor leading to potential confusion in the diagnosis of pediatric mania is the diagnostic overlap between the criteria for a manic episode and those for ADHD combined type. Although both mania and ADHD can be characterized by irritability, it is important to note that BD is classified as an episodic mood disorder, whereas ADHD is a chronic behavioral disorder. Moreover, some of the “B” symptoms are uniquely found in mania, such as hypersexuality, while other mania “B” symptoms overlap with the diagnostic criteria for ADHD (14, 15). For example, distractibility is an explicit diagnostic criterion for both mania and ADHD. Moreover, while the criterion wording is different, other symptoms of ADHD and mania appear to overlap. For example, how does one distinguish psychomotor agitation in mania from hyperactivity in ADHD? Pressured speech in mania from talking excessively, blurting out answers, and not playing quietly (ADHD)? Flight of ideas in mania from interrupting, not waiting their turn, and being “on the go” in ADHD? Thus, these diagnostic criteria often leave clinicians struggling to determine if a child has BD, ADHD, or the combination.

Beyond DSM noslogical issues, some suggest that that the increased rates of the BD diagnosis in youths is the logical extension of phenomenological studies of bipolar adults conducted during the 1980s-1990s, in which many patients reported that their first episode of mania occurred when they were a child or adolescent (16-18). Perhaps the most widely circulated example of this was Kay Redfield Jamison's An Unquiet Mind (published 1995), in which Dr. Jamison, a prominent researcher working on BD and related conditions, disclosed her own experience with BD, including the fact that her first manic episode occurred when she was a senior in high school (19). Thus, the increase in pediatric BD may represent greater awareness that serious psychopathology may present first in childhood, akin to greater acceptance in the 1980s that major depressive disorder can, and often does, present in childhood.

A third factor which may play a role in the increased numbers of children diagnosed with BD is the fact that atypical anti-psychotic medications were marketed in the 1990s to both physicians and consumers as “mood stabilizers.” Specifically, the suggestion is that clinicians may have been more inclined to diagnose children presenting with moodiness and irritability as having BD, despite not fully meeting DSM-IV criteria for a manic episode 12, because atypical anti-psychotic agents were marketed as “mood stabilizers” with few side effects and without the requirement for blood draws (unlike older agents such as lithium or valproate). In support of this position, researchers have expressed concern that the term “mood stabilizer” lacks the pharmacological precision of other medication classes, such as anti-depressant or anti-anxiety medications (21), and that such imprecision invited their use in people who are “moody” but did not meet criteria for mania. Further support comes from Olfson et al., who found that prescriptions for atypical anti-psychotic medications for children rose six-fold from 1993-2002 (roughly the same period as the rise in children and adolescents diagnosed with BD), from 201,000 to 1,224,000 prescriptions (20). Moreover,

Olfson et al. note that this rise remained in males despite controlling for other disorders which might warrant treatment with atypical anti-psychotic medications, including tic, disruptive behavior, and autism-spectrum disorders.

Nevertheless, such associational data certainly cannot demonstrate causality. With respect to Olfson's data, it remains unclear if the six-fold rise in prescriptions for atypical anti-psychotic medication for children was due to better recognition, as had occurred in pediatric depression, or an over- or misdiagnosis of BD. Indeed, arguing against a possible link between the use of atypical anti-psychotic agents and rising rates of pediatric BD, Pringsheim et al. found a 114% increase in anti-psychotic prescriptions for Canadian children (from 308,490 in 2005 to 661,300 in 2009), but most of these were for children with ADHD (17%). Such prescriptions for ADHD youth showed a consistent yearly increase. In contrast, prescriptions for youth with mood disorders represented 16% of atypical anti-psychotic prescriptions from 2005-2009, and yearly usage fluctuated up and down (21).

In sum, some speculate about a possible link between atypical anti-psychotic medication being marketed as “mood stabilizers” and the rise in children and adolescents diagnosed with BD, but the data are far from clear. However, it is clear that these medications are now FDA approved for the treatment of BD manic and mixed episodes in children and adolescents as well as the treatment of irritability associated with Autism Spectrum Disorders (22). It is also clear that there is rising concern at all levels-among parents, clinicians, researchers, the lay press, and government officials-about the growing numbers of children receiving these medications and about their now known side-effects, including metabolic syndrome and diabetes.

RESEARCH TO MOVE THE FIELD BEYOND CONTROVERSY

The rise in numbers of youth diagnosed with BD is likely to be multi-factorial. Therefore, it is important to focus on research strategies employed to move the field beyond dogma to data. This is all the more important to educate clinicians about the latest research, as they work to help families daily.

One such strategy is to clarify potential DSM noslogical ambiguity by studying rigorously the phenomenology of pediatric BD, compared to children whose primary DSM psychiatric disorder is often comorbid to BD. For example, Geller et al. conducted a multi-group study to address concerns about diagnostic overlap between pediatric BD and ADHD. She compared BD (N=93), ADHD (N=81), and typically-developing control (N=94) children and adolescents, and found that five symptoms significantly distinguished the BD from ADHD youths and typically-developing controls: 1. elation, 2. grandiosity, 3. flight of ideas/ racing thoughts, 4. decreased need for sleep, and 5. hypersexuality. Importantly, a companion article shared examples of how these symptoms would present in pediatric and adult patients with mania in comparison to how they would relate to typical development (23, 24).

Besides multi-group studies using DSM-defined groups, others have operationalized research-oriented criteria for sub-populations to advance our understanding of whether

pediatric BD is characterized by mood episodes or by chronic irritability (and related issues of how to define an episode and the inter-episode illness burden). Such criteria have also advanced our understanding of episodes of elevated/expansive versus irritable mood in pediatric BD. Among these approaches, we would like to highlight two: 1. Leibenluft et al.'s criteria for severe mood dysregulation (SMD) and 2. the Course and Outcome of Bipolar Youth (COBY) study's definition of bipolar disorder not otherwise specified (BD-NOS). Both approaches were selected because their goal is to advance our understanding of children on the edges of our diagnostic system who are often "diagnostically homeless," in that simply diagnosing them with a behavioral disorder (e.g., ADHD, ODD, or conduct disorder) does not capture the perturbation in mood noted by patients, their parents, and the clinicians working with them (25).

SEVERE MOOD DYSREGULATION (SMD) VS. NARROW-PHENOTYPE BIPOLAR DISORDER (NP-BD)

Leibenluft et al. suggested a system of putative BD phenotypes that differ in the presence of 1. euphoria vs. irritability and 2. episodic vs. chronic course (5, 26). The rationale for this approach was to facilitate pathophysiological and longitudinal research for these clinically distinct presentations, each of which may or may not ultimately represent a bipolar spectrum disorder. The most clearly "bipolar" of these presentations was defined as "narrow-phenotype pediatric BD" (NP-BD) and included children with a history of at least one episode meeting DSM-IV duration criteria of mania (seven or more days) or hypomania (4-7 days plus at least 1 major depressive episode), including functionally impairing elevated or expansive mood (euphoria) (12).

Juxtaposed to NP-BD youths, Leibenluft suggested criteria for "severe mood dysregulation" (SMD) to capture children suffering from chronic (rather than episodic) irritability (rather than euphoria) (Table 1). The SMD criteria have three central features: 1. abnormal baseline mood (anger or sadness), 2. chronic/nonepisodic irritability, and 3. ADHD-like symptoms of hyperarousal that can be confounded with some of the "B" symptoms of mania. Unlike other DSM-IV conditions where irritability is a symptom that is not defined, SMD criteria draw on affective neuroscience research to define it as "markedly increased reactivity to negative emotional stimuli manifest verbally or behaviorally."

Exclusion criteria specify that these SMD subjects cannot demonstrate cardinal features of mania, including elevated/expansive mood, grandiosity, or episodically decreased need for sleep. Unlike children with ADHD, SMD youths must have an abnormal baseline mood, whereas irritability is an associated, but not required, feature of ADHD. From the outset, Leibenluft et al. stated that it was unclear whether children with SMD have a developmental presentation of BD, an illness along the depressive spectrum, or another disorder.

Over the past eight years, Leibenluft's group at the National Institute of Mental Health Division of Intramural Research Programs has used the SMD criteria to recruit and study over 150 SMD youths (and over 150 NP-BD youths). Both SMD and NP-BD youths are similarly impaired as indicated by Children's Global Assessment Scale (CGAS) rating at initial evaluation (47.4+9.0 for SMD, 51.1+10.8 for NP-BD – both considered "moderate" impairment) as well as similar number of psychiatric medications (1.37+1.45 for SMD,

2.40+1.70 for NP-BD) and prior psychiatric hospitalizations (40.4% hospitalized at least once for SMD, 63% for NP-BD). With respect to family history, data indicate that parents of NP-BD youths were significantly more likely to have BD themselves than were parents of SMD youths (27).

To begin to address the question of whether SMD youths develop manic episodes as adults, Brotman et al. conducted a post-hoc analysis of the Great Smokey Mountain Study (GSMS), a longitudinal, population-based community survey of children and adolescents in North Carolina that started in 1992. For this study, SMD criteria were extracted from the Child and Adolescent Psychiatric Assessment (CAPA) used by the GSMS because SMD criteria did not exist when the GSMS started. Among 1,420 children participating in the first wave of the GSMS, the lifetime prevalence of SMD in children 9-19 years old was 3.3%. Most of these children meeting SMD criteria (67.7%) had an Axis I diagnosis, most commonly ADHD (26.9%), conduct disorder (25.9%), and/or oppositional defiant disorder (24.5%). In young adulthood (mean age 18.3+2.1 years), those who met SMD criteria during the first wave (mean age 10.6+1.4 years) were significantly more likely to be diagnosed with a depressive disorder (OR 7.2, CI 1.3-38.8, p=0.02) than were youths who never met SMD criteria (28). This suggests that SMD in childhood is associated with unipolar depression, rather than BD, later in life. Of note, this finding aligns with another study using data from the Children in the Community Study of 776 youths evaluated longitudinally that showed youths with chronic irritability predicted increased risk for major depression, generalized anxiety disorder, and dysthymia in young adulthood (29).

Using prospectively gathered longitudinal data from the NIMH sample, only one of 84 SMD subjects (1.2%) experienced a (hypo)manic or mixed episode during a median of 28.7 months of follow up. In contrast, 58 of 93 NP-BD participants (62.4%) experienced such a (hypo) manic or mixed episode (30). This suggests that SMD youths are unlikely to develop manic or mixed episodes. Moreover, this work should be considered preliminary, as these participants continue to be followed into adulthood and this a somewhat small non-epidemiological sample. Nevertheless, it is consistent with others' longitudinal studies confirming the association between irritability (in many cases in the form of ODD) and subsequent unipolar depression, rather than bipolar disorder (31-33).

BRAIN/BEHAVIOR INTERACTIONS UNDERLYING SMD VS. NP-BD

Beyond phenomenology, it is important to understand how the neurobiology mediating the symptoms of SMD or NP-BD may be similar or different. Towards that end, studies using affective neuroscience techniques, including out-of-scanner computerized behavioral tasks, task-dependent functional magnetic resonance imaging (fMRI), psychophysiology techniques including the measurement of evoked response potentials (ERP), and magnetoencephalography have begun to shed light on these issues. Taken as a whole, these studies have begun to show brain/behavioral alterations in SMD and NP-BD youths in cognitive processes including emotional face processing, frustration tolerance, and cognitive flexibility.

Emotional face processing is an important psychological process whose study can advance our understanding of how the pathopshyiology of SMD and NP-BD youths may be similar

or different. Studies indicate that our brains are hard-wired to respond to human faces from birth (34-37). The face serves as our canvas to display our emotional state to others, and recognition of others' emotional state based on their facial display are important parts of affect regulation (38, 39). Studies indicate that children with NP-BD make significantly more errors categorizing emotional faces than both typically developing children and those with anxiety disorders (40, 41). Similar deficits have been identified in youths who are at elevated risk for developing BD because they have a first-degree relative with BD (42). FMRI studies have shown that youths with NP-BD have altered prefrontal cortex–amygdala–striatal neural activation compared with typically developing children when viewing faces, including pictures of faces with happy, angry, or neutral emotions (43-45). With respect to SMD youths, both SMD and NP-BD participants required more intense facial displays than controls to correctly identify disgusted, surprised, fearful, and happy faces (46). However, two recent fMRI studies suggest that the neural underpinnings of face processing differ between SMD and NP-BD youths. In the first, when rating their subjective fear of neutral faces, SMD participants had significantly decreased amygdala neural activation vs. those with either NP-BD, ADHD, or typically-developing controls (47). In the second, using an implicit face-emotion processing task, NP-BD participants had significantly less amygdala activity in response to angry vs. neutral faces than either SMD or control participants (48). Taken as a whole, these data suggest that different neural mechanisms mediate face processing deficits in children and adolescents meeting either SMD or NP-BD criteria. These differences between SMD and NP-BD youths in the brain/behavior interactions underlying face processing suggest that the neurobiology underlying chronic irritability may difer from that of episodic euphoria.

Another way to advance what is known about irritability in pediatric BD is to administer computerized behavioral tasks that induce frustration via rigged feedback. From an affective neuroscience perspective, irritability can be defined as increased reactivity to negative emotional stimuli, such as frustration due to the inability to achieve a goal (26). One example of a frustration-inducing paradigm is a study by Rich et al. that paired a computerized attention task, known as the affective Posner task, with EEG recordings that allowed the measurement of ERPs (49). In this task, participants viewed a fixation cross, followed by a cue presented in one of three horizontal boxes, followed by a stimulus presented on either the left or the right side. Participants were asked to indicate which side the stimulus was on. During the first task, feedback consisted of "good job" for correct responses and "incorrect" for incorrect responses. The second task added a monetary contingency, with correct responses earning ten cents and incorrect or no responses losing ten cents. The third task added frustration to these contingencies, with 56% of trials involving correct responses receiving incorrect feedback (i.e., correct response resulting in "Wrong! Lose 10 cents!"). During the frustration condition, NP-BD youths (N=35) had lower P3 amplitude than either SMD (N=21) or typically-developing controls (N=26), reflecting impairments in executive attention in the BD group. In contrast, regardless of condition, SMD youths had lower N1 amplitude than either NP-BD or control participants, reflecting impairments in the initial stage of attention. This suggests that the pathophysiology of irritability may differ between SMD and NP-BD youths (49); in both

groups, there is attentional impairment, but the precise nature of that impairment differs between groups.

Rich et al. recently used this affective Posner paradigm and magnetoencephalography (MEG) to further advance our understanding of the pathophysiology of frustration in SMD and NP-BD youths. MEG allows neural events, such as those mediating the response to frustration in the affective Posner task, to be identified with far greater time precision than task-dependent fMRI. To do this, MEG pairs the great temporal resolution of electroencephalography (EEG) with spatial resolution of structural MRI. This study compared NP-BD, SMD, and control participants (20 in each group) during performance of the affective Posner task. Following negative feedback, NP-BD participants had greater superior frontal gyrus activation and decreased insula activation than SMD and controls, while SMD participants had greater anterior cingulate cortex and medial frontal gyrus activation than controls. In addition, SMD youths had greater self-reported arousal following negative feedback than either controls or NP-BD participants (50). These data showing that SMD youths have neural and self-reported alterations to negative feedback compared to controls suggest that these SMD youths with functionally-disabling chronic irritability have biological alterations predisposing to frustration and irritability. The fact that BD youths differ from both SMD and control participants in their neural response to negative feedback further supports the position that children with episodic euphoria and irritability are not the same biologically as children with chronic irritability.

Yet a third psychological process that can be used to probe the brain/behavior interactions underlying irritability in children and adolescents is cognitive flexibility, which refers to the ability to adapt one's thinking and behavior in response to changing rewards (51). Cognitive flexibility is relevant to BD and SMD because both conditions may involve functionally-impairing irritability. In their daily life, children with less cognitive flexibility may be less able to adapt to social feedback and rewards, such as praise or reprimand from teachers, parents or peers. In turn, they may experience frustration; as noted above, frustration can be defined from an affective neuroscience perspective as the emotional state that occurs when an individual performs an action in the expectation of a reward but does not receive a reward. Such frequent frustration may lead to functionally impairing irritability at home or school (49, 52).

Cognitive flexibility can be studied in the lab using computerized reversal learning tasks, whereby participants use trial-and-error, learning to determine which of two stimuli is initially rewarded, and then adapt their responses when the previously rewarded stimulus is now punished. Studies have shown that both NP-BD and SMD youths have impaired cognitive flexibility on reversal learning tasks, though these deficits may be more consistent among NP-BD than SMD youths (53, 54). Furthermore, a recent fMRI study showed that both SMD and NP-BD participants had similar decreases in caudate activation, vs. controls, during reversal errors, but that SMD participants had decreases in inferior frontal gyrus activation vs. both NP-BD and controls (55). Taken as a whole, this suggests that children with chronic irritability and those with episodic euphoria may both have behavioral deficits in cognitive flexibility, and that the mediating neurocircuitry is similar between groups but not identical. Ongoing studies are evaluating the specificity of these alterations compared to

youths with disruptive behavior disorders, such as ADHD, or anxiety. Ultimately, such work may suggest novel treatment targets, including both medications and psychotherapies to address specific brain/behavior alterations in cognitive flexibility and adaptability.

Work is ongoing to flesh out similarities and differences among children and adolescents meeting SMD and NP-BD criteria on these and other affective neuroscience constructs. Ultimately, such pathophysiological alterations may suggest targets for potential treatment, including medications, psychotherapies, and even cognitive remediation (i.e., using special computer games to build cognitive/emotional skills and thus “retrain the brain” and improve a child's function).

COURSE AND OUTCOME OF BIPOLAR ILLNESS IN YOUTH STUDY (COBY)

Another important approach to addressing the controversy about pediatric BD was taken by the Course and Outcome of Bipolar Illness in Youth study (COBY). Rather than creating substantially new criteria, COBY sought to determine how children with prolonged episodes of mania or hypomania fitting DSM-IV criteria were different or similar from those with more short-lived episodes.

To address this goal, the COBY study team, including sites at the University of Pittsburgh, Brown University, and the University of California Los Angeles started a multi-site longitudinal phenomenology study with support from the National Institute of Mental Health. They sought to enroll and follow longitudinally children meeting DSM-IV criteria for type I BD (BD-I; at least one manic episode lasting seven or more days) or type II BD (BD-II; at least one hypomanic episode lasting four to seven days plus at least one major depressive episode).

However, unlike other studies that excluded children whose symptoms of irritability and/or euphoria were sub-syndromal (i.e., not meeting DSM-IV definition for either BD-I or -II), COBY also enrolled children with “BD not otherwise specified” (BD-NOS). To standardize the BD-NOS group, the COBY study operationalized BD-NOS criteria that were more specific than DSM-IV's definition (i.e., those “who do not meet criteria for a specific type of BD”) (4). COBY BD-NOS criteria consisted of: A. clinically relevant BD symptoms of euphoric or irritable mood lasting a minimum of 4 hours within a 24-hour period, B. at least 2 “B” symptoms if the mood was primarily euphoric (3 if primarily irritable), and C. at least 4 cumulative lifetime days meeting these criteria.

Despite much controversy about how such BD-NOS children with frequent sub-syndromal manic symptoms would compare to more classic BD sub-types, thus far, COBY data have shown striking phenomenological similarities between those with BD-I, BD-II, and BD-NOS. At intake, COBY BD-I (N=255), BD-II (N=30), and BD-NOS (N=153) participants do not differ in age of onset of BD symptoms, duration of illness, lifetime rates of comorbid psychiatric disorders, suicidal ideation, or types of manic symptoms present during the most serious lifetime episode. In fact, elevated and/or expansive mood was found in 91.8% of BD-I and 81.9% of BD-NOS participants. However, BD-I participants had significantly more severe manic symptoms, greater overall functional impairment, and higher rates of psychiatric hospitalization, psychosis, and suicide attempts than those with BD-NOS (56).

After 4 years of longitudinal follow up, COBY study data indicate no significant between-group difference among BD-I, BD-II, and BD-NOS participants in terms of rate of recovery from the index episode (BD-I 68%, BD-II 79%), BD-NOS 66%). Interestingly, BD-II participants were significantly more likely to have a recurrence than BD-I or BD-NOS (BD-I 58%, BD-II 87%, BD-NOS 46%). Furthermore, compared to the other two groups, BD-NOS participants had significantly longer mean time to recovery from the index episode (BD-I 52.0, BD-II, 42.1, and BD-NOS 140.2 weeks) and significantly longer mean time to recurrence (BD-I 45.0, BD-II 19.0, BD-NOS 69.0 weeks). This convincingly demonstrates that the inter-episode illness burden is quite high among BD youths, regardless of whether they have full duration manic or hypomanic episodes fulfilling DSM-IV criteria for BD type I or type II, or whether they have shorter-lived episodes fulfilling COBY criteria for BD-NOS. Additionally, this suggests the possibility that BD-NOS participants have a more chronic course, despite having shorter episodes. Importantly, with longitudinal follow up, some BD-NOS participants did develop full symptoms of mania or hypomania. For example, after 4 years of longitudinal follow up, 38% of BD-NOS participants converted to either BD type I or II (57). After 5 years of longitudinal follow up, 45% (63/140) had converted from BD-NOS to either BD type I (32/63) or type II (31/63), with the strongest predictor of conversion being first- or second-degree family history of mania or hypomania ascertained at study intake (58). Taken as a whole, COBY data indicate remarkable phenomenological similarity between BD-I and BD-II youths with full-duration episodes of mania and hypomania, and those BD-NOS youths with short-lived episodes of irritability and/or elation. It also suggests the need for greater study of intra-episode mood fluctuations in BD youths, potentially employing ecological momentary analysis, as has been shown feasible in a pilot study of youths with mood disorders by Axelson et al. (59).

Hunt et al. have also recently examined COBY intake data to determine potential differences in BD youths whose most severe lifetime manic episode involved irritability only without elation, elation only without irritability, and both irritability and elation. Of 361 COBY participants, irritable-only mania was present in 10% of the sample, elation-only in 15%, and both irritability and elation in the remaining 75%. Irritable-only COBY participants were significantly younger than the other two groups, but there were no other significant sociodemographic differences. There were also no other significant between-group differences in BD subtype (I, II, NOS), rate of psychiatric comorbidities, severity or duration of illness, or family history of mania in first- or second-degree relatives. This study using the relatively large well-phenotyped COBY sample speaks to one of the major controversies about pediatric BD, namely the contention that it predominantly involves irritability rather than euphoria. Instead, these data suggest that irritable-only and euphoria-only mania are rare, with most BD youths having both (60).

POTENTIAL DSM CHANGES TO ADDRESS THE CONTROVERSY

The process of updating the DSM nosology to reflect current research on psychiatric disorders is underway as this manuscript is being prepared, with DSM-V scheduled for publication in May 2013. Until that time, it remains uncertain which proposed changes will and will not make the final cut. However, there are several potential changes related to pediatric BD that are available on the DSM-V website (www.dsm5.org). First, DSM-V

planners propose to adopt DSM-IV's “most of the day, every day” major depressive episode criteria to define mania and hypomania. A second potential change is the creation of a new diagnosis for children with chronic, nonepisodic irritability. Initially, the potential new diagnosis was known as “temper dysregulation disorder with dysphoria (TDDD).” However, based on feedback, this has been renamed “disruptive mood dysregulation disorder (DMDD).” Informed by Leibenluft's criteria for severe mood dysregulation and resultant research, this potential new diagnosis requires severe recurrent temper outbursts in response to common stressors that are out of proportion to the situation and occur three or more times per week. In addition, the mood between temper outbursts must be persistently negative (i.e., irritable, angry, and/or sad). The onset of these symptoms must be before age 10 years. The symptoms must be present for at least 12 months, with no symptom free interval lasting 3 or more months, and functional impairment must occur in two settings (and be severe in at least one). These criteria do not require the ADHD-like hyperarousal found in Leibenluft et al.'s SMD criteria. Reaction to the DSM's consideration of DMDD has been mixed. Some have expressed concern that it may be premature to add this new disorder, or that it may result in a label change (from BD to DMDD) without substantial difference in the treatment they receive or their outcome (61). Whether these and other changes related to BD in children and adolescents will make it into the published DSM-V remains unknown, though we believe it is important for clinicians to stay apprised of developments, as well as research supporting or not supporting potential changes, including by checking the DSM-V website (www.dsm5.org).

CONCLUSION

In summary, there are many reasons why increasing numbers of children and adolescents are being diagnosed with BD, most notably potential ambiguity and/or variations in how clinicians interpret DSM manic episode diagnostic criteria. To address questions about the phenomenology of pediatric BD, research has begun to examine systematically the manifestations of both episodic and chronic irritability in children and adolescents. Employing a number of techniques, from longitudinal phenomenology studies through specialized computer tasks and brain scans, these studies suggest that children with an episodic course of euphoria and/or irritability may differ from those with chronic irritability with respect to emotional face processing, frustration, and cognitive flexibility. However, these children share similar clinical attributes, including high rates of impairment, including need for psychiatric hospitalization and psychotropic medications. Ongoing and future work will address how such data can inform our diagnostic procedures as well as treatment options.

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Table 1

Severe Mood Dysregulation (SMD) Diagnostic Criteria

Inclusion criteria
1. Age 7-17 years, with symptom onset before age 12.
2. Abnormal mood (specifically, anger or sadness) present at least ½ of the day most days and of sufficient severity to be noticeable by others (e.g., parents, teachers, or peers).
3. Hyperarousal, as defined by >3: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, or intrusiveness.
4. Compared to peers, the child exhibits markedly increased reactivity to negative emotional stimuli manifest verbally or behaviorally-i.e., temper tantrums out of proportion to the inciting event and/or child's developmental stage-occurring >3 times/week during past 4 weeks.
5. Symptoms are present for >12 months without >2 months symptom-free.
6. Symptoms are severe in >1 setting and mild in a 2nd setting.
Exclusion Criteria
1. Child has any “cardinal” BD symptoms: elevated/expansive mood, grandiosity, or episodically decreased need for sleep.
2. Distinct episodes >4 days.
3. Individual meets diagnostic criteria for schizophrenia, schizophreniform disorder, schizoaffective illness, pervasive developmental disorder, or post-traumatic stress disorder.
4. Individual meets criteria for substance use disorder in the past 3 months.
5. IQ<80.
6. Symptoms are direct physiological effect of drug of abuse or general medical/neurological condition.