

The Diagnostic Dilemma:  
Why We Need to Change How We Diagnose Bipolar Disorder in Children

By Daniel Dickstein, M.D.

*Editor's note: Bipolar disorder diagnosis has been rising dramatically in children for the past decade. In response to this increase, writes Daniel Dickstein, M.D., of Bradley Hospital and Brown University, researchers at the National Institute of Mental Health and elsewhere are reviewing the diagnostic criteria. In coming years, Dickstein argues, recognizing and diagnosing bipolar disorder in children should be based more on biological markers, such as brain structure and the use of neural circuits, than on the inconsistent diagnostic categories laid out in the Diagnostic and Statistical Manual of Mental Disorders.*

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Bipolar disorder (BD) has long been among the most significant health problems for American adults, causing great impairment, including its effect on relationships, school/work, substance use, and suicide, as well as more than \$40 billion per year in health-care expenditures.<sup>1</sup> We know far less about the extent of BD in children and adolescents. Still, both clinical and research interest in pediatric BD have surged in the past two decades. Although mania—the defining element of BD—was once thought extremely rare in children, recent studies have shown that pediatric BD may be more common than once thought. For example, the percentage of minors diagnosed as having BD when discharged from psychiatric hospitals has risen from less than 10 percent in the mid-1990s to 20 percent in the mid-2000s.<sup>2</sup> Psychiatrists are not solely responsible for this increase in pediatric BD diagnosis—the incidence of pediatric outpatients receiving a diagnosis of BD has risen fortyfold during roughly the same time interval.<sup>3</sup> Clinicians, researchers, parents, and others who care for children are left wondering what accounts for this dramatic increase in pediatric BD diagnosis.

At the heart of this question lies another: Does this increase represent better recognition of an important psychiatric disorder, or does it represent overdiagnosis, misdiagnosis, or a diagnostic trend? Though this question has no simple answer, whether children receive appropriate treatment does have real-world consequences, including links between BD and suicide, substance use, academic or occupational impairment, and relationship stress.

### **Why Are More Children Being Diagnosed?**

Psychiatry's growing interest in the past 30 years in the childhood roots of mental disorders is one factor that may underlie the increase in diagnosis among young people. This increased interest is not unique to BD; for evidence that its influence cuts across almost all psychiatric disorders, look no further than the strategic roadmap of the National Institute of Mental Health (NIMH), which outlines the institute's scientific direction and funding priorities. In the early 1990s, research and lay-press publications began to note that many adults with BD recalled initial manic or depressive episodes that occurred in childhood or adolescence.<sup>4-6</sup> Following this important clinical lead, researchers began conducting studies of the phenomenology of BD in children and adolescents, including features like age of onset, impairment, and associated psychiatric disorders. Treatment studies, primarily focusing on

medications rather than psychotherapy, followed, and as these studies were disseminated, interest grew among clinicians, parents, and the public at large.

Another potential factor is psychiatric classification as codified by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). DSM-IV, published in 1994, was better than earlier editions because it emphasized the need for disorders to have symptoms that caused functional impairment. Nevertheless, two aspects of the DSM-IV manic-episode criteria may play a role in increased rates of children and adolescents diagnosed with BD: (1) duration of a manic episode, and (2) core mood features of a manic episode. DSM-IV's "A" criteria for a manic episode state that it must be "a distinct period of abnormally and persistently elevated, expansive, or irritable mood." DSM-IV further states that if this distinct mood lasts for seven or more days, it is classified as a manic episode. If it lasts four to seven days, it is classified as a hypomanic, or milder, episode.<sup>7</sup> However, it does not state how much of the day a patient's mood must be different than baseline during those four-to-seven day (hypomanic) or seven day or more (manic) episodes. If a person has a mood change for three hours every other day during a seven-day period, is that mania? In contrast, the DSM-IV "A" criteria for a major depressive episode state that it must last "most of the day, every day for two weeks," This definitional inconsistency has led to several interpretations. Some clinicians and researchers believe that BD is an episodic illness, with sustained periods (days to weeks) of mania and depression punctuating sustained periods of normal mood.<sup>8</sup> Others suggest that BD is a chronic illness, with patients fluctuating between all three mood states as rapidly as within a single day (known by some as "ultradian cycling").<sup>9,10</sup>

A second aspect of the DSM-IV mania criteria that has led to confusion is whether the "abnormally and persistently" altered mood is either elevated/expansive (also known as "euphoric mania") or if it is irritable. While a manic episode may involve function-impairing irritability, irritability is not specific to mania. Rather, it is an explicit DSM-IV diagnostic criterion for several disorders, also including generalized anxiety disorder, post-traumatic stress disorder, and, for children or adolescents, a major depressive episode. Irritability is also an associated symptom for pervasive developmental delay spectrum disorders (autism, Asperger's), attention-deficit/hyperactivity disorder (ADHD), and oppositional defiant disorder (ODD).<sup>11</sup> Yet nowhere in the DSM is irritability precisely defined. How to differentiate irritability associated with mania from that associated with another disorder (especially ADHD or anxiety disorders) or

from typical development is left to clinical judgment. Thus, some children with function-impairing irritability are being diagnosed with BD even though another diagnosis may be more appropriate.

Some researchers have speculated about a third factor potentially involved in the rising number of children and adolescents diagnosed with BD: the pharmaceutical industry. Specifically, some question the role of the pharmaceutical industry's marketing of atypical neuroleptics to physicians and directly to consumers as mood stabilizers for the expanding numbers of adults and minors being diagnosed as BD. The term mood stabilizers lacks a precise pharmacological definition<sup>13-15</sup> unlike other medications, such as anti-depressants, anti-anxiety medications, or anti-manic agents. Moreover, unlike other anti-manic medications, such as lithium or valproate, atypical antipsychotics initially did not require routine blood draws to monitor medication levels or side effects, which was appealing for pediatric patients.

During the same mid-1990s to mid-2000s period that BD diagnosis was on the rise in children and adults, the number of prescriptions for atypical neuroleptics was also increasing. Physicians from various medical specialties prescribed atypical antipsychotic medications for children 201,000 times in 1993; they wrote 1,224,000 such prescriptions in 2002.<sup>12</sup> However, in the past few years clinicians have recognized side effects of these medications, including metabolic syndrome, that now necessitate periodic blood draws. Concern about the increase in children and adolescents receiving these medications, and related concerns about overmedication or medication-related side effects such as metabolic syndrome and diabetes, has increased at all levels—parents, clinicians, researchers, the lay press, and government officials.

### **Revising the Diagnostic Criteria**

Undoubtedly, other factors underlie the growing number of children evaluated for and diagnosed with BD. In any case, one important consequence of this groundswell of interest is how research is advancing both our understanding of pediatric BD and how we think of emotional function and dysfunction in children and adolescents. Research has demonstrated that BD in children and adolescents results in considerable functional impairment, including suicidal thoughts and behaviors, reflected in high rates of psychiatric hospitalization.<sup>16,17</sup> ADHD and anxiety disorders often occur alongside pediatric BD,<sup>18,19</sup> but certain features, including euphoria, grandiosity, hypersexuality, racing thoughts, and decreased need for sleep, appear to

distinguish those with primary BD from those with primary ADHD.<sup>20,21</sup> The multisite Course and Outcome of Bipolar Illness in Youth study, supported by the National Institute of Mental Health, has followed more than 400 children with BD type I (which involves at least one manic episode lasting a week or more), BD type II (at least one hypomanic episode lasting four to seven days plus at least one major depressive episode) and BD not otherwise specified (BD-NOS) (no full-duration manic episodes). The study has shown that 25 percent of children with BD-NOS will develop full-blown BD type I or II within two years of initial evaluation.<sup>22</sup>

To address whether pediatric BD is an episodic or chronic illness involving primarily euphoria or irritability, Ellen Leibenluft and colleagues at NIMH defined criteria for a phenotype, or observable expression, of pediatric BD. Their so-called narrow phenotype included children and adolescents with clear-cut episodes of euphoric mania who all would agree had BD. Leibenluft also defined criteria for a potential broad phenotype of pediatric BD—known as severe mood dysregulation—the symptoms of which include a chronic, non-episodic course of function-impairing irritability and ADHD-like symptoms of hyperarousal.<sup>23</sup> Unlike DSM-IV, which does not clearly define irritability, Liebenluft’s criteria for severe mood dysregulation provides a definition of irritability grounded in affective neuroscience (the study of the brain and behavioral basis for emotion and emotional disorders, such as BD, using techniques including MRI brain scans, specialized computer games, and genetics): “marked 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 per week during the past 4 weeks.”<sup>24,25</sup> Such criteria have sparked an incredibly productive line of research demonstrating the similarities and differences between youths with narrow-phenotype BD and those with severe mood dysregulation. Moreover, these phenomenological differences—episodic vs. chronic course and euphoric vs. irritable mood—have sparked discussions that are relevant to clinicians and to researchers alike, as both work to understand the clinical and biological underpinnings of the disorders.

In the past decade, scientists also have gained greater understanding of the neurobiology of pediatric BD. For example, structural magnetic resonance imaging (MRI) studies have most consistently shown decreased amygdala volume in children and adolescents with BD vs. typically developing children, now shown in seven of nine cross-sectional studies.<sup>26-34</sup> Given the amygdala’s role in the processing and regulation of emotion, these findings have sparked others

to evaluate their implications by studying functional MRI (fMRI) scans and neural connectivity. Other studies have revealed decreased gray-matter volume in several other brain regions.<sup>35-37</sup>

Moreover, studies employing affective neuroscience techniques, including out-of-scanner behavioral tasks and fMRI, have advanced our understanding of the biology underlying pediatric BD. As with other neuropsychiatric disorders, this line of inquiry focuses on identifying endophenotypes of pediatric BD—behavioral manifestations of the illness that are more closely associated with genetic inheritance than the illness itself.<sup>38</sup> Simply put, it is possible that one reason why there is no single gene for BD (or for depression, ADHD, or anxiety, etc.) is because our DNA does not read the DSM. Instead, our DNA codes for certain behaviors, such as response to emotional faces or response to rewards and to punishments, that may underlie some of the individual symptoms that make up a particular psychiatric disorder. Studying these specific objectively-assessed behaviors thus holds the promise of advancing our understanding of the neurobiology of BD. Two examples of potential endophenotypes related to pediatric BD include behavioral alterations in emotional face processing and in cognitive flexibility as mediated by a specific neural circuit.

The face is among the most important emotional stimuli for humans; in our brains and in our behavior, we respond to faces from birth. Face-processing studies have been important to our understanding of BD, given that its core symptoms involve mood/emotional fluctuation. Children and adolescents with BD make significantly more errors in categorizing emotional faces in behavioral tasks than both typically developing children and those with anxiety disorders.<sup>39,40</sup> Similar deficits have been identified<sup>39,40</sup> in youths at elevated risk for developing BD by virtue of having a first-degree relative with the disorder.<sup>41</sup> FMRI studies have shown that youths with BD have altered prefrontal cortex–amygdala–striatal neural activation compared with typically developing children when viewing faces, including pictures of faces with happy, angry, and neutral emotions.<sup>42-45</sup> Taken as a whole, these studies suggest that youths with BD have fundamental alterations in the brain/behavior interactions that underlie emotional processing. Future studies could evaluate how medications or psychotherapies can ameliorate these brain/behavior alterations.

Another line of research has focused on cognitive flexibility, defined as behavioral adaptation in response to changing environmental contingencies such as rewards.<sup>46,47</sup> From an affective neuroscience perspective, many clinical symptoms of BD suggest aberrant reward

processing, including increased pursuit of pleasurable activity with high potential for painful consequences as well as increased goal-directed activity during a manic episode, and also hopelessness and an inability to experience pleasure during a depressive episode. Cognitive flexibility can be measured in lab tasks such as reversal learning paradigms, whereby participants must learn an initial stimulus/reward association and then adapt when the association is reversed. For example, if a stimulus pair consists of images of a clam and a dog, participants must first learn through trial and error that the clam is preferred (wins points) rather than the dog (which loses points). When this is reversed so that the dog is preferred, the participants must adjust. Probabilistic reward is often used to increase task difficulty—in the above example, the initially preferred stimulus (clam) might be rewarded in 70 percent of trials and punished in 30 percent whereas the initially nonpreferred stimulus (the dog) might be rewarded in 30 percent of trials and punished in 70 percent, and then the percentages are reversed. Studies have shown that youths with BD make more errors than typically developing children on both nonprobabilistic and probabilistic reversal learning tasks.<sup>48,49</sup> More recent studies have begun to explore the specificity of these behavioral deficits and to identify their neural correlates.<sup>50-52</sup> Such brain/behavior alterations in cognitive flexibility may have important treatment implications; many forms of psychotherapy, including cognitive behavioral therapy and behavior modification, require an ability to recognize and to learn from positive and negative experiences.

### **The Next Steps**

The way we diagnose BD is changing in response to research using both imaging and measures of behavior. Addressing the aforementioned discrepancy in diagnostic criteria for depression and mania, 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 in DSM-V, scheduled for publication in May 2013, is the creation of a new diagnosis known as temper dysregulation disorder with dysphoria (TDDD). While informed by Leibenluft's criteria for severe mood dysregulation and resultant research, a diagnosis of TDDD would not include the ADHD-like hyperarousal due to concerns that it would potentially lead to an increase in the diagnosis of ADHD. Whether these and other changes related to BD in children and adolescents will make it into the published DSM-V remains unknown.

NIMH is also responding to the upsurge in affective neuroscience research about pediatric BD and other conditions through its Research Domain Criteria project. Begun in 2009, the project is part of the NIMH Strategic Plan, which seeks to advance our understanding of neuropsychiatric illness by providing an alternative to categorical diagnoses inherent in the DSM approach. The Research Domain Criteria project builds on the endophenotype approach by defining basic cognitive and behavioral functions relevant to neuropsychiatric illness, such as working memory, which can be studied using cross-modality techniques from behaviors to neural circuits to genes. As part of the project effort, NIMH is seeking input, including from researchers and via conferences and workshops.<sup>53</sup>

Going forward, we need bio-behavioral markers—which a test or a scan could reveal—for psychiatric disorders, especially those in children and adolescents. Such markers would improve our diagnostic, therapeutic, and prognostic specificity. This approach is a reality in other fields of medicine, most notably oncology. Right now, cancer is diagnosed and treated using a personalized medicine approach, whereby a detailed clinical history is augmented by biomarkers, resulting in more specific and earlier diagnosis and treatment. The ultimate result is improved outcome, including less functional impairment for the patient (less time ill, improvements at work, school, and/or with relationships, and potentially a cure for some). This same personalized medicine approach could transform how psychiatric care is provided—especially for pediatric BD. The National Epidemiological Survey has shown that the prevalence of BD type I is 5 percent in people ages 12 to 29. Millions of children and adolescents who are being evaluated and treated for BD every year could benefit from this approach.<sup>54</sup> In perhaps the next five to ten years, such bio-behavioral markers combined with clinical history will result in improved, more specific, more accurate, and earlier diagnosis and treatment. Ultimately, we may be able to prevent devastating psychiatric problems including BD and reduce the suicide, substance use, academic or occupational impairment, and relationship stress that are its consequences.

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