Who Are the Children With Severe Mood Dysregulation, a.k.a. "Rages"?

One of the intents of operationalized criteria in DSM-III through DSM-IV-TR has been that different clinicians and researchers could identify the same subjects and we would know who each others' patients are (1). Although most clinicians feel they use DSM-IV criteria for diagnosis, the huge increases in rates of bipolar diagnosis made in the community over the past decade (2) suggest that clinicians may be *applying* the criteria in ways that are inconsistent. A condition that used to be characterized by discrete episodes of mania, depression, and return to premorbid personality/function (i.e., manic-depressive illness, bipolar type) is now synonymous, at least in children, with "rages." Rages are anger episodes called "mood swings" when described by parents and are explosive outbursts clearly out of proportion in both intensity and duration to the precipitant. This symptom is felt to capture the extreme irritability seen in mania. However, the irritability that often characterizes rages may occur in conjunction with many childhood disorders, most notably attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, anxiety disorders, depressive disorders, and autism spectrum disorders. One of the ongoing research questions identified by Leibenluft's laboratory in the National Institute of Mental Health's intramural program is whether there is any legitimacy to the assumption that these rages characterize a specific type of bipolar disorder in youth. By specifically defining "rage disorder" (my interpretation) with criteria and calling it "severe mood dysregulation," these researchers have made the nosologic status of rages into a testable research question by comparing the phenomenology, neurobiology, family history, and outcome of this condition with those of more historically defined bipolar disorder, what they call "narrow phenotype bipolar disorder."

"We can say a bit more, then, about who these explosive children are not. *They are* not *children at high genetic risk for narrow phenotype bipolar disorder."*

In the report by Brotman et al. in this issue, the Diagnostic Interview for Genetic Studies (3) was used to compare rates of parents' psychiatric disorders for child probands with narrow phenotype bipolar disorder and children with severe mood dysregulation. The authors in fact confirmed the familiality of early-onset bipolar disorder in those with narrow phenotype bipolar disorder and found only general population rates of bipolar disorder in the parents of children with severe mood dysregulation. We can say a bit more, then, about who these explosive children are *not*. They are *not* children at high genetic risk for narrow phenotype bipolar disorder, at least as it was ascertained by the Diagnostic Interview for Genetic Studies. Other reports from this laboratory, using data extrapolated from the Great Smoky Mountain Study, suggest that, in late teens/young adults, ADHD and depression are more likely to be found as prevailing psychiatric disorders than bipolar disorder (4). If the point of making a diagnosis of bipolar disorder in youth is to have it map on to adult data for narrow phenotype bipolar disorder I or II, a condition with a different family genetic profile and a different trajectory may have a different etiology and possibly require different treatment. This is clearly an important distinction then.

But who *are* the children with severe mood dysregulation/rages? These explosive children are not new. A closer look at the traditional diagnoses that apply to this group of

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youth gives us further insight. Although there is no significant difference in the rates of ADHD between children with narrow phenotype bipolar disorder and those with severe mood dysregulation (60.6% and 86.7%, respectively), more than twice the number of children with severe mood dysregulation have oppositional defiant disorder (39.4% versus 83.3%). Unfortunately, by examining psychopathology by diagnosis rather than by child (or adult), we miss the impact of a common and important comorbidity. Brotman and colleagues shared very salient data about children with severe mood dysregulation (personal communication, May 7, 2007). That is, rates of *combined* ADHD and oppositional defiant disorder really differ between youth with narrow phenotype bipolar disorder and those with severe mood dysregulation even more than individual disorders. Only 26.8% of the children with narrow phenotype bipolar disorder had this toxic combination, compared to 80.8% in those with severe mood dysregulation—virtually three times as many! Why is this important? It emphasizes that the confusion between uncomplicated or mild ADHD and mania is probably a red herring. No clinician confuses uncomplicated ADHD with mania! It is the *combination* of the disinhibition of ADHD and irritability of oppositional defiant disorder (relevant criteria are "often loses temper; often argues; is often touchy or easily annoyed") that is confusing. At a minimum, it is the combination of ADHD and oppositional defiant disorder that should be compared with mania, and controlled for severity of symptoms as well (5). If we recast children with severe mood dysregulation as children with prominent combined ADHD and oppositional defiant disorder, we find we have considerable knowledge about them already. For instance, follow-up studies do not report inordinate rates of narrow phenotype bipolar disorder in children with ADHD plus oppositional defiant disorder. However, conduct disorder (CD) and later antisocial behavior/criminality and substance abuse are the unfortunate legacies of combined ADHD and oppositional defiant disorder (ODD) (6). Waschbusch et al. (7) further describe youth with this comorbidity as having the pathological feature of "aggressive response to low provocation not found in either ADHD-only or in ODD/CD-only boys." This certainly sounds like severe mood dysregulation. Focusing on the term "aggression," especially reactive/impulsive aggression, reveals another large literature—one with equally sobering results. Affective, impulsive aggression, especially when severe, remains a chronic problem in a sizable number of children from preschool through late adolescence at least (8). However one defines it, rages, severe mood dysregulation, ADHD plus oppositional defiant disorder, or reactive/affective/impulsive aggression, children with this constellation of symptoms, even if narrow phenotype bipolar disorder does not eventuate, are likely headed for trouble and misery. It is worth remembering, moreover, if these symptoms are co-occurring with narrow phenotype bipolar disorder, it is likely to worsen the prognosis of that condition as well.

A second point to be made in this editorial regards the family history findings and the Diagnostic Interview for Genetic Studies. Although this instrument is quite comprehensive in its coverage of adult psychopathology, it severely short-changed child psychopathology (and thus the validity of the data emanating from it) by not asking about many childhood disorders, as noted by Brotman and colleagues in their discussion of the study's limitations. For instance, Table 2 shows that parents of raging children have much lower rates of psychopathology than parents of children with narrow phenotype bipolar disorder. That is a rather staggering finding! Most studies of children with ADHD and oppositional defiant disorder find high rates of psychopathology in family members (9). If children with severe mood dysregulation are basically mood-dysregulated children with ADHD plus oppositional defiant disorder, we would certainly expect to find ADHD, oppositional defiant disorder, conduct disorder, and antisocial personality disorder in their families—unless, of course, no one asked about these conditions. On the other hand, if rates of psychiatric disorder are truly that much lower in the parents of children with severe mood dysregulation, perhaps many of these youngsters will

have transient, stress-related, developmental problems that will not impair them in the future. We will never know since the interview did not ask, and not asking is not the same as not having.

Finally, not only may specific comorbidities be relevant for bipolar disorder in probands, they may also define genetic subtypes in their family members (10). If there are plans to modify the Diagnostic Interview for Genetic Studies, some questions involving childhood disruptive behavior and developmental disorders should be included.

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