# Defining the Boundaries of Childhood Bipolar Disorder

Pediatric bipolar disorder is notoriously controversial, with the epicenter of the debate being whether the condition can be diagnosed in prepubertal children at all. Some clinicians avoid labeling affectively labile youngsters with bipolar disorder, preferring instead less stigmatizing categories like depression, ADHD, or the ubiquitous yet vacillating "mood disorder not otherwise specified." Others diagnose prepubertal bipolarity rather liberally, often based solely on the presence of irritability, mood swings, and aggression. At stake is whether the childhood presentation of bipolar disorder represents the same disorder as in adults. If the same, then euphoria, grandiosity, and classic manic symptoms might be required (the narrow phenotype conceptualization [1, 2]). If different, then perhaps irritability and nonspecific mood lability would suffice (the broad phenotype [3]). These terms represent more than semantic differences, laden as they are with implications for treatment, prognosis, and genetic and neuroimaging research.

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In favor of the narrow phenotype, one might argue that diagnostic conservatism is justified given few available effective mood stabilizers and their greater risks in children compared with adults (e.g., a higher incidence of Stevens Johnson syndrome associated with lamotrigine [4] or of hepatitis with valproate [5]). Further, absence of sharp diagnostic refinement could confound studies looking for relevant genes or neural circuits. Finally, if we call admittedly different symptom constellations by the same name, could we not be misleading patients and families?

By contrast, and in favor of the broad phenotype, it might be argued that the childhood presentation of *any* mental illness is different during childhood, simply due to age-dependent neurobiological and psychosocial changes. In this view, if development is compromised by serious psychopathology, assertive treatment would be warranted, and precision in nomenclature a secondary consideration.

An advocate of the broad phenotype need not invoke childhood exceptionalism, for a similar dilemma exists with adults: is a broad bipolar spectrum valid nosologically (as proposed by Emil Kraepelin in his original manic-depressive illness concept [6]), or should we maintain the narrow definitions of bipolar disorder currently favored in DSM-IV? Although certainly not without critics, such a viewpoint can be defended by an accumulating literature in adult bipolar disorder indicating that irritable and mixed phenotypes of mood are quite common, perhaps more so than pure mania or pure depression (7, 8). If this is correct, then the controversy in children would perhaps not be about childhood presentations per se, but rather about the larger issue of whether the broad definition of the bipolar spectrum is valid (9). Incidentally, some have argued—and not entirely without a point—that the broadening of the bipolar diagnosis is the handiwork of the pharmaceutical industry (10). And yet, we doubt that many pharmaceutical detail men called on Kraepelin one hundred years ago, when he first advanced the concept that bipolar disorder was more spectral than categorical (11).

The most widely accepted approach to validate the boundaries of psychiatric disorders follows the criteria established by Robins and Guze (12). It is based on the accrual of data from five independent lines of evidence, namely symptoms (phenomenology), course of illness, familial clustering, treatment response, and biological markers. The

fact that there are five sources of evidence, and not just one, is critical. This reality reflects the often underappreciated antiessentialism of psychiatric diagnoses (13): no single criterion is essential to most psychiatric conditions, and thus we need to look for a constellation of evidence, rather than for any one pathognomonic clincher. If this fact were better understood, clinicians would perhaps avoid many a fruitless debate.

While the Robins and Guze approach has been used to validate DSM-III and IV, it has not been quite reflected in DSM criteria themselves: DSM-IV relies almost entirely on cross-sectional phenomenology as the one validator for its diagnostic criteria for primary psychiatric conditions (noteworthy exceptions being schizophrenia and PTSD, with their course and etiology criteria, respectively). By relying mainly on DSM-IV's cross-sectional phenomenological approach to diagnosis, opponents often end up splitting nosological hairs over whether certain symptoms represent prepubertal mania or ADHD.

Family history, although often complicated by patterns of comorbidity, can be particularly helpful given the usual availability of parents and other relatives for interview, and given the fact that longitudinal course data are in shorter supply. Sometimes treatment response can be used to confirm or refute diagnoses, but this is perhaps the most nonspecific diagnostic validator, since medications are often effective in multiple conditions (e.g., antidepressants) or even in enhancing normal mental states (stimulants). And while poor treatment response or adverse reactions might also be diagnostically informative, such as in the case of antidepressant-induced mania (14), the logic is insufficient, if not faulty, in retrofitting a diagnostic category to a treatment response.

The remaining major diagnostic validator, that of biological markers, is the one explored for pediatric bipolar disorder in the report by Rich and colleagues in this issue of the *Journal*. In it, investigators at NIMH enrolled children (mean age=13 years) from three primary diagnostic groups: 1) narrow-phenotype bipolar disorder (having had at least one episode of mania or hypomania as specified in DSM-IV); 2) severe mood dysregulation (nonepisodic irritability, hyperarousal, and overreactivity to negative emotional stimuli at least three times weekly); and 3) healthy comparison subjects. Among the children with bipolar disorder or severe mood dysregulation, there was extensive comorbidity with ADHD and anxiety disorders. The children with severe mood dysregulation were more likely to fulfill criteria for major depressive disorder and oppositional defiant disorder as well. Psychotropic drug administration was much more common among those with bipolar disorder and was not stopped for the study.

The investigators conducted an experimental task in which children reacted to visual targets flashed on a computer screen, earning rewards of 10 cents for each correct response. In the critical part of the test, called a frustration task, even correct answers were arbitrarily judged as too slow, which the subjects indeed found frustrating. The purpose was to elicit negative emotional reactions, which were rated higher in both patient groups than in the healthy subjects. During the test, the investigators recorded visual evoked potentials to the targets and found that, relative to healthy comparison subjects, the bipolar group had lower P3 wave amplitudes during the frustration task, which have been reported in adult bipolar disorder and are thought to represent a defect in executive function. The severe mood dysregulation group had an entirely different deficit, a diminished N1 wave in all phases of the test, which is thought to indicate lower attention paid to the stimuli. The aim of the experiment was not to construct an electrophysiological test for diagnosis but rather to determine if the clinical difference in diagnosis was mirrored by an underlying difference in brain pathophysiology. The investigators conclude that the two groups are indeed different and suggest that severe mood dysregulation, particularly when accompanied by oppositional defiant disorder, is biologically different from pediatric bipolar disorder.

In examining these psychophysiological differences between broad and narrow bipolar phenotypes, the investigators' efforts do not simply accept, but rather *test* DSM def-

initions, as the framers of DSM-III originally hoped for. The research team found that narrow-phenotype bipolar disorder appeared biologically similar to adult bipolar disorder. The chronic irritable broad phenotype did not, and seemed instead to overlap with oppositional defiant disorder. We note that for a condition that has been so singularly divisive, it is only poetic justice that of all things a *frustration* task was used to elicit differences in the event-related potentials at the core of the experiments.

In assessing any study, one should assess its methods not simply against a gold standard ideal study but also against the current state of the literature. Given much heat and little light in childhood bipolar nosology, this article represents hard-earned and legitimate progress. However, in the future, other studies should attend to at least two methodological issues that could advance our knowledge even further. First, in this study, the broad bipolar phenotype was defined as chronic irritability, but *episodic* irritability may be more relevant (15). Further, the study excluded children with episodic decreased need for sleep from its broad bipolar phenotype, even though this neurovegetative feature may hold the key to identifying children with nonclassic bipolar disorder (16). The key issue may not be overreactivity to stimuli (as in this article) but rather *hyper*activity (a general state of increased energy/decreased need for sleep). Whether this important feature differentiates bipolar disorder from ADHD in particular was not explicitly addressed.

Second, all nosological studies are observational; there is no way to randomize a nosological study. Hence confounding factors—other differences between the groups besides the topic being studied—may account for the results (17). In this study, only age was statistically controlled; other differences such as gender and treatment were not, and many other potentially relevant variables (socioeconomic status, presence of psychosis, comorbid medical illnesses, concomitant psychosocial stressors, and history of physical or sexual abuse) were not assessed. Thus, the results observed may be related to the two diagnostic phenotypes, or again they may not. At present, this is what we have, and we should use it with an open mind, aware that much is likely to change in the years ahead. For one, evoked potentials technology undoubtedly will continue to be refined, and sophisticated new methodologies to characterize behavioral phenotypes and endophenotypes increasingly will become available.

What might the practicing clinician conclude? Chronic irritable mood does not appear to be sufficient to justify a bipolar disorder diagnosis, but it still remains possible that an *episodic* irritable phenotype would biologically correlate with the narrow bipolar disorder phenotype. It remains to be seen whether, as some suspect, some instances of oppositional defiant disorder or ADHD represent childhood harbingers of what ultimately evolves into recognizable bipolar disorder in adulthood. While we wait for newer data, we would urge clinicians to focus on diagnosis and then to seek proven treatments, rather than to engage in a simplistic and potentially risky symptom-ameliorating polypharmacy. The Hippocratic tradition of caution in the face of uncertainty, combined with the modern emphasis on diagnosis, may be the wisest course to take (13).

In closing, we believe that it is time to emerge from the current diagnostic Tower of Babel and to strive for a unified language: research in juvenile bipolar disorder might look to the history of autism for a lesson. A balkanized approach to diagnosing the pervasive development disorders had stymied progress in that field until consensus guidelines were developed, an accepted set of standard instruments were uniformly embraced, and grassroots efforts from invested parents provided the critically necessary thrust. The high public visibility of juvenile bipolar disorder, the efforts of dedicated though hardly synchronized research groups, and the role of vocal parents committed to the welfare of their affected children, could combine to deliver the flashpoint for a new phase in the research agenda for this condition. Convening a group of investigators and stakeholders to establish consensus diagnostic guidelines would be a natural place to start.

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