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News Focus

BIPOLAR DISORDER: Poles Apart

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The number of children and adolescents diagnosed with bipolar disorder has been rising sharply, prompting debate and research on how the illness should be characterized in young people

Bipolar disorder used to be considered a disease of adulthood. Most mental health professionals assumed that the first episode of mania--the defining event for the illness--rarely occur red before people reached their 20s and might not hit until middle age. It came as a surprise to some, then, when two studies published last year documented a dramatic increase over a decade in the number of children identified with the disease.



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A U.S. survey* revealed that in 2003, 1% of the population under 20 received the diagnosis--a 40-fold leap since 1994. Another study[†] indicated that up to five times as many U.S. children and adolescents were hospitalized for bipolar illness in 2004 as in 1996. No one knows for sure "whether there is an increase in these very disturbed kids or whether they are being relabeled," says psychiatrist Gabrielle Carlson of Stony Brook University School of Medicine on Long Island.

Critics of psychiatry such as psychiatrist David Healy of Cardiff University in the U.K. attribute at least part of the increase to the influence of the pharmaceutical industry, which they believe leads to over-diagnosis by encouraging doctors to prescribe the latest drugs for problem children.

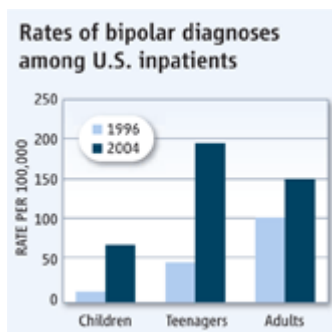
The debate has been fueled by recent allegations that Harvard University psychiatrist Joseph Biederman, a leading proponent of the idea that many childhood disorders are actually bipolar illness, has received substantial support from drug companies. Biederman, who says "there were no conflict-of-interest violations" in his ties to industry, insists that the increase in diagnoses more closely reflects the real incidence of the disease. "I spend my days dealing with these populations" of troubled children at Massachusetts General Hospital (MGH) in Boston. "I can tell you it's a very desperate state of affairs."

Other researchers agree that the numbers don't exaggerate the problem. "We don't go out in the street and offer meds to children," says psychiatrist Christoph Correll of the Albert Einstein College of Medicine in New York city. "They are sent to us."

The stakes are high. A wrong diagnosis could consign a person to decades of inappropriate drug treatment; failure to spot the disease can lead to many years of misery--as was the case with child actress Patty Duke, who recounted at this year's annual meeting of the American Psychiatric Association (APA) in Washington, D.C., that she suffered for more than 15 years before being diagnosed with bipolar disorder at age 35. But getting the diagnosis right is difficult because there are no objective tests for bipolar disorder, and the disease in children can look very different from that in adults.

An upward trend

The disorder used to be known as manic depression. The change in name was sparked in part to avoid the somewhat derogatory word "manic" but also for accuracy. A person's primary tilt may be toward one or the other mood extreme--more often, depression--although mania is the tip-off. The trouble is, it's often hard to distinguish mania from a welter of other symptoms and problems, especially in children. Even in adults, bipolar disorder, estimated to afflict about 1% of the population, has been called "the great impersonator" because it comes in many guises and often coexists with other problems, says psychiatrist Husseini Manji of the U.S. National Institute of Mental Health (NIMH) in Bethesda, Maryland. And it's especially complicated because it's marked by two drastically different mood states: profoundly debilitating and often-suicidal depressions and intense phases of manic hyperactivity.



CREDIT: SOURCE: CDC

With children, the disease is even more complex. They're "a moving target" when it comes to mental disorders, says Correll. Their fast-developing brains are unpredictable. They have difficulty expressing themselves, they have little or no history to guide the clinician, and it's often impossible to tell whether some behavior is pathological or just a twist in the path of normal development. What's more, children's symptoms do not simply mimic those of adults. Children are more likely to have "mixed" states that combine euphoric and destructive behavior.

Partly for these reasons, it was not until 1995 that members of the Pediatric Psychopharmacology Unit at MGH published a paper suggesting that many children who were then being identified as hyperactive or having conduct disorders were in fact bipolar. Judging by the leap in diagnoses over the following

decade, that finding resonated with pediatricians, says co-author Janet Wozniak, head of MGH's pediatric bipolar research program. It also jibes with recent studies of adult bipolar patients indicating that about 60% of them experienced the first symptoms before age 18.

These troubled children are not just fidgety, noisy, whiny, sulky, or contrarian. They may be angry and self-destructive, prone to violent rages or dangerous impulses such as jumping out of a moving car during an argument, exhibit sexually inappropriate behavior, and risk losing touch with reality, says psychiatrist Barbara Geller of Washington University in St. Louis, Missouri. Geller adds that mania in a child may initially be hard to differentiate from childish giddiness. These children are "never serious, always acting up--they've been described by many parents as behaving as if they're little Jim Carreys," she says. But there's an added element of grandiosity: "They'll get up and start teaching the class or tell coaches how to coach."

Such symptoms may seem distinctive, but mania is hard to recognize when it's mixed with a half-dozen other problems that youth is heir to. *The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, psychiatry's bible, contains many labels that could fit a troubled, acting-out child. Most common is attention deficit hyperactivity disorder (ADHD). Others include conduct disorder; anxiety disorders, including obsessive-compulsive disorder; and newer diagnoses such as "oppositional defiant disorder" and "intermittent explosive disorder."



Delayed diagnosis. Former child star Patty Duke, now 61, was diagnosed with bipolar disorder at the age of 35. In her late teens, she told psychiatrists at their May meeting, she experienced "eruptions of temper alternating with taking to bed for months at a time, getting up only to go to the bathroom and attempt suicide."

CREDIT: HULTON ARCHIVE/GETTY IMAGES

Narrow versus broad constructionists

Clinicians roughly divide into two schools of thought over how broad a range of behaviors should be classified as bipolar, says Carlson. In an online seminar this year sponsored by the American Academy of Child and Adolescent Psychiatry ("What those in the know, know," www.aacap.org), Carlson described two cases that illustrate the challenge.

One child, 13-year-old "Nicola," is brought in by her parents because of a sudden behavior change over the previous 2 or 3 weeks. Formerly quiet, she is suddenly loud and grandiose, donning sexy clothing, talking constantly, and sleeping little. Her moods have become volatile, and she is easily driven to hysterical laughter or frustrated rages.

The other, "Lynda," 11, has been hyperactive since preschool, a condition that has been helped somewhat by stimulants (Ritalin). But lately it's gotten worse, and she has become unruly, explosive, aggressive, and provocative in her dress and behavior. She's developed some new habits including downloading porn on the computer and smoking marijuana. At the same time she's anxious and depressed, and she's falling behind in school.

Are one or both of these girls bipolar? Some researchers, including a group at NIMH, take a conservative approach to the diagnosis. In the seminar, psychiatrist Ellen Leibenluft says she would diagnose Nicola as bipolar, tipped off by the sudden change in her personality. But Lynda's symptoms are not episodic, which the NIMH group believes is central to a bipolar diagnosis. To them, the problem looks like severe mood dysregulation (SMD), a category that Leibenluft's group has created to describe mood and behavior problems that persist over a number of years.

The group at MGH, however, would diagnose both girls as bipolar. Wozniak puts more stock in Lynda's chronic irritability and explosive rages. Biederman, her boss, says such children have often been labeled as having ADHD. Yet, he says, ADHD is not fundamentally an emotional problem, and children like Lynda "are all the time in [emotional] turmoil." It's "very clear," says Biederman, that "these children had every symptom in *DSM* of mania." It's just that they may have a lot of other things wrong as well. Psychiatrist Boris Birmaher of the University of Pittsburgh School of Medicine in Pennsylvania says, "I see the same [type of] kids as Biederman," but he doesn't believe they're all bipolar. One way to assess the probability in a given case, he says, is to look at what's going on with a child's first-degree relatives. The disease is highly heritable, and studies have shown that the risk goes up 10-fold if a person has a bipolar parent.

Carlson is also skeptical of Biederman's assessment. Bipolar children tend to grow into bipolar adults, she notes. Yet, "so far, what we know from long-term studies of ADHD and aggressive children" suggests that many of the type who might now be diagnosed as bipolar children grow up to be substance abusers, hotheads, and antisocial personalities--but not bipolar. Carlson is co-author of a forthcoming paper on a 23-year follow-up of 101 "high-risk" children into adulthood. Although all had big problems, she says, only "one-third of those with what some call a 'bipolar phenotype' developed adult-style bipolar disorder."

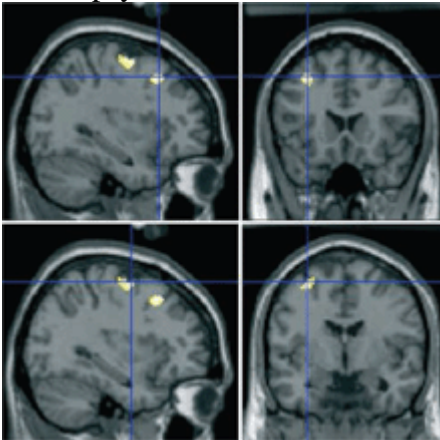
"Getting this [bipolar] diagnosis means putting people on meds for life," says Manji, "so you kind of want to be sure we're treating the right thing." Missing a diagnosis of bipolar disorder can also have serious repercussions: If a bipolar child is given medication for just ADHD, that can trigger mania, as can antidepressants. If someone is suspected of being bipolar, says Wozniak, they should be started on a mood stabilizer (lithium or an antiseizure drug) before getting medications for other conditions. And other drugs--for depression, anxiety, or ADHD--are almost always necessary. The average pediatric bipolar patient, clinicians say, is usually on three or four drugs.

The bipolar brain

Right now, physicians must make a diagnosis solely on behavioral symptoms: There is no test available for bipolar illness. Gene hunts have failed to come up with more than a list of possible suspects. And brain-imaging studies often produce conflicting information.

Nonetheless, comparisons of brain functions between bipolar children and those with other diagnoses are yielding some intriguing clues that could eventually help in diagnosis. Psychiatrist Daniel Dickstein, formerly with Leibenluft's NIMH group and now at Brown University, thinks bipolar children have a deficit in the brain's "reward machinery." Mania, he says, is a "hyperhedonic" state in which the brain is "excessively reward-sensitive." Depression is the converse. He believes that teasing out different brain

responses to a test involving rewards may help differentiate the brain mechanisms of bipolar illness from those of other psychiatric illnesses in children.



Bipolar brain. Images show significantly greater activation in both the prefrontal cortex (top two panels) and primary motor cortex (bottom two) in 25 young people diagnosed with bipolar disorder than in controls matched by age, sex, and IQ. Activation in the prefrontal area also differentiated bipolar youth from those with severe mood disorder (SMD), according to research in press.

CREDIT: NELSON ET AL., *BIPOLAR DISORDERS* 9, 810-819 (2007)

The task Dickstein has used to probe these brain mechanisms assesses "reversal learning." In this test, two groups of subjects are compared on a task in which they are rewarded for matching certain cards according to color, number, or shape; they have to learn by trial and error when rules are covertly changed by the experimenter. Fifty children aged 7 to 18 who exhibited classic cyclical bipolar illness--the kind readily recognizable in the *DSM-IV*--were compared with 44 others whom the NIMH group labeled as SMD: chronically irritable, agitated, and with ADHD-like symptoms. Both groups did worse than the controls on the tests, but the bipolar group--even though they were tested when in a normal mood--made more errors and took longer to learn the new rule (*Journal of the American Academy of Child and Adolescent Psychiatry*, March 2007). This indicates they have a harder time inhibiting a learned response that is no longer rewarded and replacing it with a new one that is. That, says Dickstein, suggests impaired "cognitive flexibility."

In as-yet-unpublished work, the NIMH group claims that brain imaging further bolsters this theory. Leibenluft reported at this year's APA meeting that the two groups could be distinguished on the basis of parietal lobe activity in response to a "change task" that requires subjects to switch gears cognitively, inhibiting one response and substituting a new one.

Another type of task is designed to reveal poor regulation in both cognitive and emotional circuitry--as evidenced by lack of cognitive flexibility and emotional overreactivity. This is a frustrating computer game in which subjects are initially rewarded for speedily hitting the right button in a test; later they discover that no matter how fast they respond, they are told they lost because they weren't fast enough.

During the test, Leibenluft and Brendan Rich compared a particular brain wave--the P3 wave, which reflects focused attention in the parietal lobe--in bipolar and SMD children compared with a group of normal controls. Both the bipolar and SMD groups reacted with more frustration than did the controls, the group reported in February 2007 in *The American Journal of Psychiatry*. But the brain waves of the bipolar children looked different. The amplitude of a much-studied brain wave, P3, was lower in this group, suggesting, says Leibenluft, that they weren't able to "mount the extra attentional effort" needed to overcome their emotional frustration.

Other probes reinforce the picture of poor emotional regulation with bipolar illness. In a study also headed by Rich and published 6 June 2006 in the *Proceedings of the National Academy of Sciences*, Leibenluft's group compared brain images of 22 adolescents with 21 controls in reaction to images of

facial expressions. There were no differences between the two groups in looking at a nonemotional facial feature: nose width. But those with the bipolar diagnosis saw more anger in the neutral faces and reported more fear when viewing them--showing correspondingly more activation in emotional brain areas, particularly the amygdala, the seat of fear.

Some researchers suspect that bipolar disorder is linked to more far-flung perturbations in the nervous system. Dickstein, for example, thinks it may affect fine motor movements. He led a study comparing bipolar children, bipolar children who also had ADHD, and children diagnosed with just ADHD. The results, published in *Biological Psychiatry* in October 2005, indicated that the bipolar groups--both with and without ADHD--were slower than the ADHD group on a test that involved touching one's thumb to each of the four other digits in sequence and repeating the process four times, a chore that requires both motor and cognitive flexibility.

Some scientists also believe that bipolar illness is linked to problems that extend beyond the nervous system to the endocrine and immune systems--as hinted by the fact that bipolar people have more than their share of other health problems, such as obesity, diabetes, hypothyroidism, migraine, and multiple sclerosis.

Researchers believe that studying the disease in its earliest stages will be necessary to figure out what's really going on. Says Wozniak: "If it comes on in childhood, it stands to reason that starting our studies with children will yield better results. Symptoms in adults are complicated by meds and by years and years of illness. Studying them is like studying cancer only in the end stage."

*C. Moreno *et al.*, *Archives of General Psychiatry*, September 2007.

†J.C. Blader and G. A. Carlson, *Biological Psychiatry*, 15 July 2007.