

Treatment in Psychiatry begins with a hypothetical case illustrating a problem in current clinical practice. The authors review current data on prevalence, diagnosis, pathophysiology, and treatment. The article concludes with the authors' treatment recommendations for cases like the one presented.

Treating the Childhood Bipolar Controversy: A Tale of Two Children

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Children for whom the differential diagnosis includes bipolar disorder and/or attention deficit hyperactivity disorder (ADHD; combined type) are usually complex and present thorny assessment and treatment problems. The cases of “Seth” and “Eric” illustrate these issues. They are presented in tandem to illustrate how information might unfold and how the flow of information directs treatment in situations where the question of bipolar disorder and/or ADHD is raised.

Background Information on Seth

Seth, age 10, was referred by his school principal for his impulsive behavior (e.g., pulling fire alarms), aggressive behavior (e.g., pushing everything off the principal's desk and trying to tip it over when brought to his office), and frequent outbursts. His outbursts consisted variously of cursing and screaming, hitting others and himself, and throwing objects. They occurred several times a week when he felt thwarted, insulted, or provoked. His mother was frightened for the safety of Seth's younger sisters. When seen for emergency consultation, Seth appeared agitated and had rapid, pressured, off-topic speech. He claimed that he did not remember what happened in the principal's office.

Intake information revealed that Seth had been a mildly language delayed, hyperactive, dangerously impulsive toddler who could not sleep at night. By age 4, he had experienced many moves and observed domestic violence. In his Head Start program, he began to throw “megawatt fits.” Methylphenidate made his behavior worse, and by age 5 a diagnosis of bipolar disorder was made because of his rages. Subsequently, he was treated unsuccessfully with risperidone, aripiprazole (which caused a 40 lb weight gain), divalproex, oxcarbazepine, and topiramate, ultimately arriving at his current regimen, which consisted of 25 mg of atomoxetine, 0.1 mg of clonidine, and 25 mg of lamotrigine, all administered nightly.

Seth's mother had experienced a postpartum depression. His father had numerous learning disabilities and a substance abuse problem. They were divorced.

Background Information on Eric

Eric was also age 10. Consultation was sought because of his unpredictable, explosive behavior and extremely

low frustration tolerance. He too was severely hyperactive and impulsive, and he had fine motor problems. Because he was close to grade level, his school was unwilling to provide services. He had taken mixed amphetamine salts from ages 5 to 9; this medication was stopped when his aggressive outbursts intensified and a diagnosis of bipolar disorder was made. He was then treated with a series of atypical antipsychotics and anti-convulsants, together and separately, but his behavior and performance deteriorated so badly that he could not be maintained in school. Eric's outbursts occurred when he was asked to work in school or do homework, when he wanted something that his teachers or parents would not give him, and during transitions from subject to subject in class or when asked to go anywhere without being given a great deal of warning.

Other than being very fidgety and easily distracted and repeatedly asking when the interview would end, Eric's mental status was normal.

Eric's daily medication regimen consisted of 750 mg of divalproex and 400 mg of quetiapine.

Eric's maternal grandmother had bipolar I disorder, which was treated successfully with ECT. His father had a childhood history of ADHD and had been in recovery from alcohol and cocaine abuse for 10 years.

The Clinical Problem

Seth and Eric highlight the “bipolar disorder versus ADHD” or “bipolar disorder and ADHD” controversy in preadolescent children. They both had symptoms of ADHD, but they also had symptoms of severe mood lability, inadequate response to ADHD treatment (or any other medication for that matter), and family histories of mood disorders. Youngstrom et al. (1) attribute some of the bipolar/ADHD controversy to researchers' use of different conceptualizations of bipolar disorder, different diagnostic interviews, and different criteria to define study samples. They also note that researchers' definitions may alter the DSM-IV criteria and do not necessarily reflect how the diagnosis is used in clinical practice.

The question of the prevalence, pathophysiology, and treatment of bipolar disorder in children (versus adolescents) will obviously depend on how one diagnoses it. Literature review is unhelpful since most authors combine child and adolescent data or data on bipolar I disorder, bipolar II disorder, and bipolar disorder not otherwise specified. Whether research groups have used more liberal or more conservative definitions of episodes, euphoria, and grandiosity, they can marshal data to validate their approach.

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Besides the question of how broadly or narrowly to define mania in youths, there is the related question of how to diagnose children with explosive, aggressive behavior. Previously these symptoms in children were included within the broad definition of hyperkinesis, the predecessor of ADHD. Laufer and Denhoff (2) described “behavior of almost volcanic intensity” and changeability such that the child could be “sometimes good and sometimes bad.” In DSM-III, this emotion component of hyperkinesis was split off from the “core” attention and hyperactivity symptoms, and the explosive, aggressive behaviors were absorbed into the “associated symptoms” of ADHD, oppositional disorder/oppositional defiant disorder, and conduct disorder. Investigators of aggression have developed their own terms—“affective,” “impulsive,” or “hot” aggression—which appear to identify the explosive behavior manifested by children usually with symptoms of ADHD (3). Leibenluft et al. (4), exploring differences between children with episodic mania and those with chronic explosive behavior, called the latter “severe mood dysregulation.” This is distinguished from mania by the absence of episodes, euphoria, and grandiosity and the presence of prominent and chronic (at least 1 year) anger/irritability or sadness, with severe tantrums occurring several times a week in multiple settings. Other symptoms that may be seen in both mania and ADHD—insomnia, distractibility, flight of ideas, pressured speech, and intrusiveness—are also present. More than 80% of these children have comorbid ADHD and oppositional defiant disorder (5).

Although debate rages about whether severe ADHD symptoms, fluctuating behavior, and short temper with significant aggression represent a virulent form of ADHD or a juvenile subtype of bipolar disorder, there is an evidence base, albeit a small one, for treating both conceptualizations—that is, mania with or without ADHD as well as ADHD with explosive aggression. Thus, practice parameters (6) and consensus documents (7) suggest that in bipolar disorder mood and/or mania should be treated first, and if ADHD symptoms remain, they should be addressed with evidence-based treatments for ADHD. Most of the data for effective treatments for mania in children (down to age 10) and adolescents come from FDA-requested, industry-sponsored studies of medications approved for mania in adults. Data have been published or presented demonstrating that for acute or mixed mania, about 50% of the patients treated with olanzapine, risperidone, quetiapine, or aripiprazole improve about 50%, compared with a response of about 25% with placebo (8, 9). Results for divalproex are mixed (10, 11), and results for other mood stabilizers (e.g., oxcarbazepine) are disappointingly negative (12). A large-scale placebo-controlled study of lithium is under way, but at this time the only similar study

that has been conducted on acute mania in children and adolescents with lithium was negative (13).

Treatment for ADHD includes stimulant medications or atomoxetine, behavior modification, and academic accommodations if needed (14); data also suggest that in cases where ADHD is accompanied by extreme aggression in the absence of a mood disorder, stimulants are somewhat beneficial (15–17). There is, in fact, a mandate to begin controlled studies of children whose aggression is not satisfactorily addressed by ADHD treatments alone (3).

There have been three small but systematic studies indicating that the addition of ADHD medications to anti-manic medications in children with bipolar disorder and ADHD does not worsen symptoms and may improve them (18–20). There have been no studies of atomoxetine in comorbid ADHD and bipolar disorder.

Circumstantial evidence indicates that even for children with manic-like symptoms, stimulants alone generally do not cause children to develop bipolar disorder (21–23), and where there is evidence of poor response or worsening of symptoms, the implications are non-specific in that such responses may occur in any number of conditions (24–26). There are anecdotal reports of atomoxetine-induced mania in children with ADHD, but to date, placebo-controlled trials of children with ADHD and depression have not provided evidence of a placebo-drug difference (27). The phenomenon of switching and drug-induced disinhibition is difficult to study (28), and non-stimulant treatment of ADHD needs such attention.

Finally, evidence suggests that atypical antipsychotics, lithium, stimulants, and valproate are effective for treating aggression (29). The ADHD practice parameter thus recommends the addition of these medications to ADHD treatments for patients who have ADHD plus aggression (14).

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Applied Assessment and Treatment

Diagnosis Expectations

Until we truly understand early-onset bipolar disorder, it will be important to acknowledge the different viewpoints about the condition and to determine both what parents' understanding is and why they want to know whether the diagnosis pertains to their child. For instance, Seth's mother had been told that his rages had prompted the bipolar disorder diagnosis. She had not described manic episodes—that is, distinct periods when Seth's mood was clearly different from usual, lasting at least several days with concurrent elation/irritability, grandiosity, and accelerated verbal and physical activity. Rather, she noted that he became incredibly enraged for up to an hour when he did not get his way, was disappointed, or felt insulted. Some investigators (30) would concur that this presentation is likely bipolar disorder; others (4) would not diagnose bipolar disorder in the absence of discrete manic

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episodes. Seth's mother wanted to know if he really had bipolar disorder in order to "find the right medication."

Eric's bipolar disorder diagnosis was made by his referring clinician after the apparent worsening of his symptoms on stimulant medication, and it was additionally supported by his positive family history. Unlike with Seth, in Eric's case there appeared to be a distinct period, after he began treatment with a stimulant, in which his mood was markedly worse than usual, although it was not clear whether this period met other DSM-IV criteria for a manic episode. Regardless, some investigators view increased irritability on stimulants and other medications as evidence of a manic switch, which is especially portentous in the context of a family history of bipolar disorder (31). Unlike Seth's mother, Eric's parents wanted to know their son's trajectory. Current treatment was also important, but the long-term implications concerned them more.

Comprehensive Assessment

Comprehensive, standardized parent and teacher rating scales are an important preliminary part of an ADHD evaluation (14). Screening measures have likewise been advocated for bipolar disorder (6). The best screens cover the important comorbidities and "rule-outs," including ADHD, oppositional defiant disorder, conduct disorder, anxiety and depressive disorders, psychosis, tic disorders, autism, and, of course, mania. These measures do not make a diagnosis but, accurately completed, alert the clinician to important problem areas to be pursued further.

Seth's ratings showed parent and teacher concordance for high levels of hyperactivity, impulsivity and distractibility, oppositional defiance, conduct disorder, generalized anxiety, and deviant language items (rapid, excessive, off-topic speech). There were differences in mania ratings on the Child Mania Rating Scale (32), however. A parent score of 16 was made up of items reflecting irritability, explosive behavior, distractibility, and rapid speech. (Often it is helpful to know not only a score but what items were rated to achieve the score.) The teacher score was 24, reflecting, in addition to irritability and explosiveness, periods when Seth was "wound up and excited" or had higher than usual energy. Like Jensen et al. (33), we find that the reasons ratings are discordant, in this case between parent and teacher, are as informative as specific scores. For instance, Seth was explosive both at home and at school, but his teacher noted additional symptoms. We need to know *why* there is a discrepancy between his mother's and his teacher's ratings.

Seth's school report underscored a notable disability in math and written expression, which had been present since first grade. He had a full-scale IQ of 84, with especially poor performance in working memory and processing speed.

Eric's ratings evidenced different inconsistencies between parents and teachers. His parents noted manic and depressive symptoms in addition to severe ADHD and oppositional defiant behavior, whereas his teachers endorsed only ADHD and oppositional defiance. Eric, previ-

ously at grade level, experienced a drop in grades over the past several years. It will be important to try to understand why.

Parent and Child Interview

Although interviews developed for the study of mood disorders in children have good reliability, what is rarely discussed is the fact that reporting on one's own behavior may pose a difficult cognitive task, and both parent and child reports can be profoundly influenced by question wording, format, and context (34).

Seth's Mood Disorder History and Mental Status

Even after careful questioning, Seth's mother did not make a case for episodes (distinct periods of markedly different mood than usual) of mania or depression. On the other hand, she was so overwhelmed and immobilized by Seth's behavior, and so desperately wanted him out of the house, that Seth's psychiatrist did not feel that her information was diagnostically reliable.

Nor was Seth able to shed light on his "mood swings," since he denied or forgot them. He did appear agitated during the interview. His language impairment was obvious but could have reflected manic flight of ideas or (recall that Seth was also language delayed) the chronic problems with pragmatic language seen in some children with ADHD (35). His cognitive difficulties may have precluded his being able to truly understand the intent of questions about mania or depression. Note that the mental status examination is more than a cross-examination of the child about symptoms; it is an opportunity to observe his mood, relatedness, language, and thinking ability.

For safety and diagnostic reasons, Seth was hospitalized and taken off medication while further information and observations were obtained. The working hypothesis was that he had ADHD, oppositional defiant disorder, and severe mood dysregulation (based on the frequency and severity of his explosiveness, the presence of other ADHD symptoms, and the absence of clear episodes), although bipolar disorder had not been ruled out.

Eric's Mood Disorder History and Mental Status

Although Eric's parents had endorsed many manic symptoms on rating scales, they had not really understood the intent of the questions. The example given for elated mood was how excited Eric got when his parents capitulated to his relentless demands. Indeed, it sounded like he got more excited than the situation warranted, but the thrill was short-lived. They agreed that he was often silly, but the silly behavior was clearly attention-seeking, not motivated by feeling wonderful or euphoric. This behavior had caused peers to think of him as "immature," and indeed, his silly behavior tended to be annoying, rather than infectiously funny, as one often sees in hypomanic or manic children or adults. Eric did become explosive when told "no," but that had been a lifelong response. As he had gotten physically bigger, the damage he inflicted was also greater. His parents also thought his wish to continue playing instead of going to bed was evidence of decreased need for sleep. In this case, not only was the problem chronic but when he

did manage to wangle a later bedtime, he was tired and even more grumpy the next day.

A careful medication history revealed that Eric's stimulant appeared to have become less effective by the time he was in third grade. Increased academic demands exacerbated his frustration and led to outbursts in school and at home. Stimulant-induced hypomania had probably not occurred. When Eric's referring psychiatrist changed Eric's diagnosis to bipolar disorder, stimulants were replaced with other medications, as recommended in guidelines for bipolar disorder (6), but Eric's behavior deteriorated further.

Eric candidly said that he knew if he persisted long enough in nagging his parents, they would relent. If that did not work, he would become enraged. While he felt bad for the trouble he caused, he felt entitled to what he wanted. This entitlement had been called grandiose by his parents. He was very distressed in school because he could not pay attention, was constantly in trouble, was rejected by peers, and hated anything to do with written work, such as homework, since he could barely print, let alone write. He described himself as more happy than sad, but he often felt discouraged. He did not meet criteria for major depression or dysthymic disorder.

The hypothesis was raised with Eric's parents that his worsening behavior in third grade may have resulted from frustration stemming from the increased demand for written work, homework, and more mature social skills. In addition, he had developed what has been called a "coercive relationship" with his parents (36). That is, his behavior was so toxic that his parents gave in, rewarding his outbursts and teaching him that aggressive behavior was how to get what he wanted. His grandmother's history of bipolar I disorder had raised the specter of bipolar disorder, which was one reason his stimulant medication was stopped; yet his behavior and academic performance deteriorated further, and none of the bipolar treatments had helped. Bipolar disorder could not unequivocally be ruled out, but Eric's history suggested a diagnosis other than mania.

Treatment and Discussion

Seth's Treatment and Follow-Up

Seth was admitted to the hospital, his medications were discontinued, and he was observed with standardized ratings for a week. His score on a nurse-rated Child Mania Rating Scale was similar to the parent-rated score of 16. Depressive symptoms were not observed. Seth learned that there were consequences for his outbursts and was able to control them better. Seth's mother was given the skills and backup needed to make it clear that such behaviors would not be tolerated at home.

Academically, Seth was woefully behind and needed a less frustrating academic placement than the one he was in.

Seth had unequivocal symptoms of ADHD, which were treated with mixed amphetamine salts since his mother was convinced that methylphenidate had made his behavior worse. This treatment reduced but did not eliminate his distractibility, impulsivity, and excessive talking.

After several weeks of gradual improvement, Seth's behavior suddenly worsened. He became more disruptive at bedtime, and he responded explosively to any kind of limit. The positive relationship with his teacher became a

wild crush, and he began writing hundreds of incoherent poems to her. When the attending psychiatrist showed an interest in the poems, Seth redoubled his efforts. His rapid speech increased, and he responded to interruptions with anger. His weekly nurse-rated Child Mania Rating Scale score was 38, made up of observations indicating increased irritability and energy (despite decreased sleep), elevated mood, rapid and pressured speech, grandiosity, and erotic and hypersexual behavior.

Several explanations of Seth's behavior were entertained, including the possibility that his previous improvement had simply been a "honeymoon" (37), that the mixed amphetamine salts had induced mania, or that he was spontaneously experiencing a manic episode. A call to Seth's outside teacher confirmed that she had observed similar episodes prior to the start of stimulant medication. Seth's mother agreed and was now able to distinguish mania from symptoms of ADHD plus oppositional defiant disorder. Thus, the rating scale differences were now explained.

Neither increasing the dosage of Seth's stimulant medication nor stopping the medication altered his behavior. He was impervious to the behavior management plan. Given a persistently elevated mood over a 1-week period, in tandem with increased energy and signs of hypersexuality, Seth was considered to be exhibiting a DSM-IV manic episode. Lithium was started both because it had never been tried and because his mother did not want him to take an atypical antipsychotic again. His behavior continued for several weeks and clearly constituted an episode different from his "usual" self—which, we had seen, was already compromised by his ADHD, oppositional behavior, and difficult home situation.

On lithium, Seth's behavior eventually improved, but not enough for his mother to manage. Since the alternative was residential placement, his mother agreed to the addition of risperidone (0.5 mg twice a day). On risperidone, Seth's irritability diminished further. Mixed amphetamine salts were started again, which improved his concentration; repeat IQ testing revealed a 16-point increase, mostly due to improvements in working memory and processing speed.

Seth was discharged to a combined behavioral program and a special education setting, on a regimen of 1200 mg of lithium daily, 0.5 mg of risperidone twice a day, and 15 mg of mixed amphetamine salts twice a day. His discharge diagnoses were bipolar disorder, most recent episode manic; ADHD, combined type; oppositional defiant disorder; reading and math disorder; and language disorder not otherwise specified. Since Seth clearly had more than bipolar disorder, attention to all of his challenges was necessary. He has remained stable for a year but continues to need treatment. His mother was advised that he indeed had bipolar disorder but that medication continuation should be decided on a year-to-year basis rather than worrying about the need for medication for "the rest of his life."

Eric's Treatment and Follow-Up

Eric's parents were relieved to learn that he might not have bipolar disorder and that ADHD is as heritable as bipolar disorder (both have a heritability ratio of about 0.8 [38]). They understood that they had not caused Eric's problem but had possibly exacerbated it, and they agreed that he needed a different medication approach,

stability and consistency at home, and appropriate expectations and placement at school.

Eric's previous treatment trials suggested that medications had been adequately dosed and tried for reasonable lengths of time. Thus, his lack of response to medications was not due to poor management. The decision was made to obtain behavior ratings of Eric's ADHD symptoms and ratings of the frequency and severity of outbursts while on his current regimen, and then to stop his medications and observe him for deterioration; if there was none, methylphenidate would be used alone initially. His behavior did not worsen appreciably off quetiapine and divalproex.

Although long-acting stimulant medications are usually preferred in order to avoid the need for an in-school midday dose, Eric's insurance would only cover the much less expensive, short-acting form. Nevertheless, at 20 mg of methylphenidate three times a day, Eric's behavior and academic performance in school improved. He was also placed in a smaller classroom with more support for written work and for difficult behavior. His outbursts diminished but did not disappear, and his parents now bore the brunt of these at home when the last dose of his medication had essentially worn off (Eric could not tolerate an evening dose). The addition of aripiprazole, more consistent child management techniques, and the threat of hospitalization helped somewhat, as did the fact that school was more satisfying and that he had made a few friends. Eric's referring physician continued to seek a medication that was as helpful in the evening as methylphenidate was during the day. Eric's final diagnosis was ADHD, combined type; oppositional defiant disorder; severe mood dysregulation; and disorder of written expression.

Conclusion

There are important reasons why mania and severe ADHD should be understood as different conditions. However, from a therapeutic standpoint, the difference between mania and severe ADHD (plus aggression) is not in the use of atypical antipsychotics and mood stabilizers, both of which are supported by a substantial evidence base for use in both disorders. Nor is it in the need to provide psychoeducation and specific parenting help for families. There is a robust literature on behavioral treatment for ADHD and a growing literature on psychosocial treatments for bipolar disorder (39). Although the terms used to describe interventions to control dysregulated mood and aggressive behavior are different, many of the actual interventions are similar. Two of the most substantial differences in treatment are whether or when to treat ADHD and how to advise parents and child about future treatment.

As we have seen, both Seth and Eric had a long history of ADHD, a volatile temper, and problems with mood regulation, overwhelming parents and teachers alike. Both were significantly challenged academically and had more than ADHD. The diagnosis of bipolar disorder rests on demonstrating an episode, a sustained period of behavior that differs from the person's usual self, in which elated/expansive/irritable mood co-occurs with other symptoms that

operationalize the accelerated energy, thinking, and hyperhedonic activity that underpin mania. Seth was actually observed to have such a period lasting several weeks during which he appeared different—that is, excessively elated, even more explosive than previously, grandiose, and “constructively” energetic (in contrast to his background hyperactivity), with changes in sleep behavior. Once these features were pointed out, his teachers and his mother confirmed that they had occurred previously.

A case might be made that Eric also had an episode, starting around third grade, when his behavior worsened. His aggression and frustration intolerance increased, but he did not experience a simultaneous co-occurrence of other manic symptoms. His ADHD was inadequately treated, but his psychiatrist, concerned about his family history of bipolar disorder, chose to initiate treatment for that disorder.

Both Seth and Eric, even when treated with the best medication and parent and school interventions, remained somewhat symptomatic, which illustrates the fact that we simply do not yet have completely effective treatments for many children with this constellation of symptoms and behaviors.

In diagnosing bipolar disorder in children, it is necessary to keep an open mind, and to continue to do so after the first interview; ongoing observation is critical. A family history of bipolar disorder is important but does not, in and of itself, make a diagnosis. A full assessment, using multiple informants, is needed to address differential diagnosis, including learning and language disorders. Ultimately, it is important to understand the child, not just to reach a diagnosis.

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