Current PSYCHIATRY

CASES THAT TEST YOUR SKILLS

Two weeks after changing medications, a hyperactive 11-year-old becomes manic and attempts suicide. Is the new regimen or an undiagnosed mental disorder to blame?

A 'bad' boy's behavior problems

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HISTORY IMPULSIVE AND DISTRACTIBLE

For 2 years Mark, age 11, has been treated for attention-deficit/hyperactivity disorder (ADHD). His initial symptoms included inattention, hyperactivity, distractibility, short attention span, failure to follow instructions, poor organization, and intruding on others. He often picks fights with his 7-year-old brother, mildly injuring him on one occasion. His teacher recently punished him for roaming the classroom and distracting his classmates.

None of Mark's symptoms suggest mania. His family has no history of mood disorders, but his father has been diagnosed with substance dependence.

Mark's psychiatrist had prescribed an extended-release amphetamine salts preparation, 10 mg/d. Soon after, Mark began experiencing stomachaches, insomnia, facial flushing, and headaches. The dosage was reduced to 5 mg/d, but Mark stopped taking the medication after less than 3 weeks. Cognitive-behavioral therapy and classroom modifications were then tried for 11 months, but Mark's behavior worsened. His symptoms now include inattention, distractibility, excessive talking, restlessness, and impulsivity.

How would you treat Mark?

- **try another stimulant**
- **switch to nonstimulant ADHD medication**
- **treat with mood stabilizer**
- **re-evaluate initial diagnosis**

The authors' observations

Children and adolescents often present with excessive talking, distractibility, increased activity or restlessness, and loss of normal functioning. Distinguishing these ADHD symptoms from those of bipolar, disruptive, learning, movement, anxiety, substance-related or other mental disor-

Table 1

FDA guidelines for monitoring pediatric antidepressant use

After starting an antidepressant, patients should see their doctor:

- Once weekly for 4 weeks
- Every 2 weeks for the next month
- At the end of the 12th week taking the drug
- More often if problems or questions arise

Source: Reference 8

Box 1

Youths with ADHD, depression may also have mania

As many as 20% of children diagnosed with ADHD also meet DSM-IV-TR criteria for bipolar disorder.

When bipolar disorder is the initial diagnosis, 30% to 40% of adolescents and 70% to 90% of prepubertal children may meet ADHD criteria.

Prepubescent major depression carries a 50% lifetime risk of developing mania.

Source: References 3, 11-13

ders can be challenging.[1] Youths with these symptoms often are misdiagnosed, leading to inappropriate treatment.

Mania may resemble ADHD or co-occur in children with ADHD more often than previously thought.[2-4] Distinguishing mania from ADHD is important because an antidepressant or antidepressant-like medication may induce mania in a youth with diagnosed or undetected bipolar disorder—especially if a mood stabilizer is not used. Using stimulant medications to treat ADHD in a child with bipolar disorder also may unmask or activate manic symptoms. (See "How to reduce mania risk when prescribing stimulants," October 2005, at www.currentpsychiatry.com.)

Pediatric bipolar disorder often goes undetected because DSM-IV-TR criteria—established for adults—may not apply to youths. Children are more likely to present with a mixed mood state, less-distinct periods between episodes, grandiosity, irritability, and a chronic, continuous course.[2] By contrast, bipolar adults often present with a sudden classic manic episode, elation, and euphoria.[2] Adults also usually have relatively stable periods between episodes and tend to have comorbid substance dependence, panic, or eating disorders.

Mark's symptoms still suggest ADHD. His inattention started before age 7, and his teacher is mostly concerned about his hyperactive, impulsive, and disruptive behavior. Mark's mother, teacher, and psychiatrist feel confident that the ADHD diagnosis is correct, so we decide against comprehensive reassessment or prescribing a mood stabilizer. Mark's mother opts to try the nonstimulant ADHD medication atomoxetine rather than a different stimulant.

TREATMENT A MOVING EXPERIENCE

Mark's psychiatrist prescribes atomoxetine, 18 mg/d for 4 days, then increases the dosage to 25 mg/d after finding that the boy could tolerate the medication.

Two weeks after starting atomoxetine, Mark becomes agitated and activated, and voices suicidal thoughts on one occasion. Without warning, while his mother is driving him to school, he opens the door of the moving vehicle and tries to jump out. His mother stops him by calling his name, yelling "No," and slamming on the brakes. Mark tells her that he is "bad" and wants to die. She has no idea what prompted this behavior.

Mark also has become more oppositional and defiant, and his temper tantrums and destruction of household items are more frequent. He continues to behave aggressively toward his younger brother, often breaking some of his favorite toys. Mark also shows elevated and expansive mood, irritability,

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pressured speech, inflated self-esteem, and psychomotor agitation—symptoms consistent with a manic episode. At one visit, Mark tells his psychiatrist, "I feel great! I can do anything."

Mark's symptoms now suggest:

- **medication-induced switch to manic episode**
- **medication-induced suicidality**
- **emergence of manic symptoms independent of medication**

The authors' observations

Mark, who had been diagnosed as having ADHD, began showing manic activation and suicidal thinking 2 weeks after starting atomoxetine. Whether he showed de novo suicidal behavior or reckless behavior associated with mania is unclear.

Atomoxetine-induced mania is not a new finding.[2,5] During clinical trials, 2% of patients reported mood swings and 8% reported irritability. Subsequent experience indicates the risk of mood destabilization may be as high as 33%.[5]

Atomoxetine, a nonstimulant medication indicated for treating pediatric and adult ADHD, is a potent norepinephrine reuptake inhibitor. Reanalysis of the atomoxetine clinical trial database showed a slightly but statistically significant higher risk of suicidal behavior and thoughts in children and adolescents compared with placebo.[6] No deaths from suicide were reported. The FDA subsequently ordered a black box warning on atomoxetine's label instructing physicians, patients, and families to watch closely for suicidality symptoms with atomoxetine use.

Atomoxetine is safe and effective for pediatric ADHD, provided youths are properly monitored. Be careful, however, when prescribing atomoxetine to youths with a personal or family history of mood disorder.

FDA also is reviewing data on all drugs indicated for treating ADHD to determine whether they cause suicidality, new-onset mental disorders, or other psychiatric adverse events.[7]

Box 2

FDA: 12 features that suggest suicide risk

- New or more thoughts of suicide
- Suicide attempts
- New or worsened depression
- New or worsened anxiety
- Feeling agitated or restless*
- Panic attacks
- Difficulty sleeping (insomnia)*
- New or worsened irritability*
- Aggressive, angry, or violent behavior*
- Acting on dangerous impulses*
- Extreme hyperactivity in actions and talking (hypomania or mania)*
- Other unusual behavior changes*

* Suggest both ADHD and mania
Source: References 8-10

ASSESSING MEDICATION RISK

All youths being treated for a mood disorder and/or ADHD must be assessed for suicide risk, but how to most effectively perform this assessment is unclear. Organizations representing pediatrics and child and adolescent psychiatry have not yet incorporated FDA's medication guidelines regarding pediatric suicidality—released earlier this year—into their guidelines (*Table 1, page 78*). As a result, most physicians follow pediatric patients less frequently than FDA now advises.

Atomoxetine's receptor profile resembles that

Table 2

What to include in an ADHD evaluation

Histories: psychosocial, developmental, medical, educational, substance use and/or family

Clinical interviews with the child or adolescent. Corroborative interviews with parents, guardians, teachers, others

Rating scales assessing past behavior: Instruments completed by multiple sources such as the youth, family members or guardian, former teachers, others

Rating scales of current behavior: Instruments completed by youth, parents or guardian, former teachers, siblings, significant others

Psychological testing: Psychoeducational evaluation, personality inventory, intelligence assessment, and/or a continuous performance test. ADHD diagnosis remains clinical, and no evaluation should rely too heavily on "objective tests" for a definitive diagnosis

of antidepressants, which also are labeled with a black box warning describing increased suicidality risk when used in children and adolescents. Risk of suicidal behavior is highest within 10 days of starting antidepressants, and a significant risk remains throughout the first month. The suicidality rate appears to drop after that time.[9,10]

How would you have handled this case?

Visit www.**currentpsychiatry**.com to input your answers and compare them with those of other readers

Follow FDA patient monitoring guidelines for antidepressants when prescribing atomoxetine to youths—particularly given the prospective labeling change. Atomoxetine's manufacturer is expected to release a patient monitoring guideline unique to this drug.

SUICIDALITY: FINDING OTHER CAUSES

Suicidality is more prevalent in bipolar disorder than in other mental disorders,[2,4] and ADHD and mania often co-exist (*Box 1, page 78*).[11,12] Mania induced by medication might explain suicidality or other behavior changes in some youths, but activation, mania, behavior change, or suicidality can result from the primary or comorbid disorder rather than the medication.

No deaths by suicide were reported among the FDA-reviewed studies of antidepressant use in children and adolescents. Fatal suicidal behavior has been reported in adolescents not treated with medications.[14]

FDA cites 12 features that point to suicide risk in youths (*Box 2, page 87*).[8-10] Seven features suggest both ADHD and mania, which overlap to the point of diagnostic distraction.

What strategies can help psychiatrists distinguish ADHD from mania in suicidal youths?

- **observe for elated mood and/or grandiosity**
- **confirm course of illness, looking for pre-existing depression**
- **check for irritable hyperactivity**

The authors' observations

Consider a broad differential diagnosis when evaluating inattention, hyperactivity, and impulsivity in children. Family medical history, corrob-

orative clinical interviews, past and current behavioral rating scores, and psychological testing can help confirm an ADHD diagnosis (*Table 2*).

A careful patient interview, watching for diagnostic clues, taking a confirmatory history, and attention to key symptoms can help you discern ADHD from mania. Rule out unexplored diagnoses such as substance abuse, disturbed relationships, medical illness, and other mental disorders. Having the family and teachers track the youth's longitudinal mood, energy, sleep, and actions may confirm a mood disorder.

Elated mood or grandiosity indicate mania. Irritable hyperactivity is seen more frequently in mania, whereas general hyperactivity tends to be present in ADHD. Childhood depression often heralds bipolar disorder.

Suspected medication-induced suicidality may call for stopping the offending agent, but determining whether a mental disorder or medication is causing suicidal thoughts can be difficult.

Try stopping the suspected offending drug first. If the youth remains suicidal after 1 week, a thorough biopsychosocial reassessment may guide future options including inpatient care, intensive outpatient psychotherapy, monitoring, and cautious use of antidepressant and/or antimanic medications.

Suicide risk requires clinician vigilance. As we learn from the FDA's warnings, each treatment episode confers new risk and underscores the importance of watching for risk factors that may predict suicide (*Table 3*).

Table 3

Risk factors that may predict suicide in youths

Older (pubertal) age
Male gender
Mania
Mixed mood state
Psychosis
Victim of sexual or physical abuse
Co-occurring disruptive disorders
Comorbid substance abuse
Impulsivity
Easy access to means, such as firearms, lethal toxins, or medications
Lack of family support
Acute stressors
Family history of suicide

Source: Adapted from reference 2.

CONTINUED TREATMENT NO MORE MEDICATION

Mark's psychiatrist immediately stops atomoxetine. The boy's mother, a psychiatric nurse, declines a trial of divalproex because she fears drug toxicity. Mark's suicidality and agitation resolve over 1 week, and he returns to baseline function, leading us to believe his mania was medication-induced.

One year later, Mark takes no medications. He is behaving well at school and made the honor roll this fall. His teacher reports that Mark is "smart, well liked, but talks excessively," though she says his talking is "not as out of control" as it was a year ago.

Mark recently began playing soccer as an outlet for his hyperactivity. He has not been penalized on the soccer field but is occasionally "over the edge," pushing and shoving other players. When frustrated at

Bottom Line

Determining whether bipolar mania or a medication is causing suicidality in children and adolescents can be difficult. Try stopping the suspected offending drug first. If the youth remains suicidal after 1 week, a biopsychosocial reassessment can help determine the next course of treatment.

Related resources

- U.S. Food and Drug Administration. List of drugs receiving a boxed warning, other product labeling changes, and a medication guide pertaining to pediatric suicidality. www.fda.gov/cder/drug/antidepressants/MDD_alldruglist.pdf.
- Eli Lilly and Co. Questions and answers about the Strattera (atomoxetine) label change: a guide for patients and parents. www.strattera.com/1_5_news/Q&A_Strattera_label_update.pdf.
- U.S. Food and Drug Administration. Public health advisory: Suicidal thinking in children and adolescents being treated with Strattera (atomoxetine). www.fda.gov/cder/drug/advisory/atomoxetine.htm.
- Mann JJ, Apter A, Bertolote J, et al. Suicide prevention strategies: a systematic review. *JAMA* 2005;294(16):2064-74.

DRUG BRAND NAMES

Divalproex sodium • Depakote
Mixed amphetamine salts • Adderall XR
Atomoxetine • Strattera

DISCLOSURE

The authors report no financial relationship with any company whose products are mentioned in this article, or with manufacturers of competing products.

home he has short outbursts, slams doors, and yells at his brother without being physically aggressive.

Mark's office visits are infrequent, but he recently asked his mother to take him to his psychiatrist and counselor. His mother realizes he may soon need medication, but she wants to wait.

References

1. Rappley MD. Clinical practice: attention deficit-hyperactivity disorder. *N Engl J Med* 2005;352:165-73.
2. Kowatch RA, Fristad M, Birmaher B, et al. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2005;44:213-35.
3. Scheffer RE, Apps JN. ADHD or bipolar disease? Age-specific manic symptoms are key. *Current Psychiatry* 2005;4(5):42-52.
4. Schapiro NA. Bipolar disorders in children and adolescents. *J Pediatr Health Care* 2005;19:131-41.
5. Henderson TA, Hartman K. Aggression, mania, and hypomania induction associated with atomoxetine. *Pediatrics* 2004;114:895-6.
6. Eli Lilly and Co. Questions and answers about the Strattera (atomoxetine) label change: a guide for patients and parents. Available at: http://www.strattera.com/1_5_news/Q&A_Strattera_label_update.pdf. Accessed Oct. 16, 2005.
7. Mathews AW, Abboud L. FDA offers more details on relabeling: concern that ADHD drugs may cause adverse events stemmed from few reports. *Wall Street Journal* June 30, 2005:D4.
8. U.S. Food and Drug Administration. The FDA required medication guide about using antidepressants in children and teenagers. Available at: http://www.fda.gov/cder/drug/antidepressants/SSRIMedicationGuide.htm. Accessed July 1, 2005.
9. U.S. Food and Drug Administration public health advisory October 15, 2004: Suicidality in children and adolescents being treated with antidepressant medications. Available at: http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm. Accessed July 1, 2005.
10. U.S. Food and Drug Administration public health advisory: Labeling change request letter for antidepressant medications. Available at: http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm. Accessed July 1, 2005.
11. Wozniak J, Biederman J, Kiely K, et al. Manic-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry* 1995;34:867-76.
12. Biederman J, Faraone S, Mick E, et al. Attention-deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? *J Am Acad Child Adolesc Psychiatry* 1996;35:997-1008.
13. Wozniak J, Spencer T, Biederman J, et al. The clinical characteristics of unipolar vs. bipolar major depression in ADHD youth. *J Affect Disord* 2004;82 (suppl):S59-S69.
14. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA* 2004;292:338-43.