ADHD symptoms are stable, then a sudden relapse

Muhammad Hassan Majeed, MD, and Muhammad Khalid Zafar, MD

How would you handle this case?

Answer the challenge questions throughout this article

R, age 11, has ADHD, which has been stable on extended-release methylphenidate. Over 2 months, hyperactivity, inattention, and impulsivity reemerge. What could be causing his symptom relapse?

CASE Sudden deterioration

R, age 11, has attention-deficit/hyperactivity disorder (ADHD), combined type, and oppositional defiant disorder, which has been stable for more than a year on extended-release (ER) methylphenidate (brand name: Concerta), 54 mg/d (1.2 mg/kg). With combined pharmacotherapy and behavioral management, his symptoms of hyperactivity, inattention, and impulsivity improved at school and at home. He shows some academic gains as evidenced by improved achievement at school.

Over 2 months, R experiences a substantial deterioration in behavioral and academic performance. Along with core symptoms of ADHD, he begins to exhibit physical and verbal aggression. A report from school states that R has been using obscene language and destroying property, and has had episodes of provoked aggression toward his peers. His grades drop and he receives 2 school suspensions because of aggressive behavior.

What could be causing R's ADHD symptoms to reemerge?

a) nonadherence to treatment
b) substance abuse
c) medication change
d) all of the above

The authors' observations

Worsening of psychiatric symptoms in a stable patient is relatively common. Many factors can contribute to patient destabilization. Treatment nonadherence is a leading cause, along with psychosocial stressors and substance use (***Table***).

EVALUATION Adherence confirmed

R is hyperactive and distracted during his visit, a clear deterioration from his baseline status. R is oppositional and defiant toward his mother during the session, but shows good social skills when communicating with the physician.

R's mother reports that her son seldom forgets to take his medication, and she ensures that he is swallowing the pill, rather than chewing it. Data from the prescription drug-monitoring program show that the family is filling the prescriptions regularly. The ER methylphenidate dosage is raised to 72 mg/d. The clinicians provide psychoeducation about adherence to a medication regimen to R and his family. Also, his parents and teachers

Dr. Majeed is Attending Psychiatrist, Natchaug Hospital, Mansfield Center, Connecticut. Dr. Zafar is Child and Adolescent Psychiatry Fellow, Drexel University, Philadelphia, Pennsylvania.

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receive Vanderbilt Assessment Scales for ADHD to assess the symptoms in different settings.

At a follow-up visit a week later, R's mother reports that her son continues to have problems in school and at home. The Vanderbilt scales reveal that R is having clinically significant problems with attention, hyperactivity, impulse control, and oppositional behavior.

A urine drug screen is ordered to rule out the possibility of a sudden deterioration of ADHD symptoms secondary to substance use disorder. To ensure compliance, we recommend that R take his medication at the school nurse's office in the morning.

A week later

Although R takes his medication at school, he continues to show core symptoms of ADHD without improvement. The urine drug screen is negative. A physical examination does not reveal any medical illness. The treatment team calls the pharmacist to obtain a complete list of medications R is taking, who confirms that he is only receiving ER methylphenidate, 72 mg/d. The pharmacist also notes that R's medication was switched from the brand-name drug to a generic 3 months ago because of a change in insurance coverage. This change coincided with the reemergence of his ADHD symptoms.

R's mother reports that the new pills do not look like the old ones even before the dosage was raised. A new brand-necessary prescription is sent to the pharmacy. With the brand-name medication, R's symptoms quickly improve, and remain improved when the dosage is decreased to the previous dosage of 54 mg/d.

With osmotic-controlled release oral delivery system (OROS) and outer coating of ER methylphenidate, how much drug is released immediately vs slow release?

a) 22% immediate release and 78% slow release

b) 78% immediate release and 22% slow release

c) 50% immediate release and 50% slow release

Table

Considerations in patients whose symptoms have worsened following an initial stabilization

Nonadherence or partial adherence to treatment
Comorbid psychiatric or substance abuse disorder
Psychosocial factors or stress
Complicating physical health problems (eg, hypothyroidism or hyperthyroidism and temporal lobe epilepsy)
Drug–drug interactions (eg, inhibition of stimulant effect of amphetamines by lithium, introduction of a medication that competes with cytochrome P450 2D6-dependent metabolism)
Brand vs generic bioavailability
Decrease in effective weight-based dose secondary to growth in pediatric patients

The authors' observations

Generic substitution of a brand medication can result in worsening of symptoms and increased adverse effects. Possible bioequivalence issues can lead to failure of drug therapy.[1]

In 2013, the FDA determined that 2 specific generic formulations of ER methylphenidate do not have therapeutic equivalency to the brand-name medication, Concerta. The FDA stated, "Based on an analysis of data, FDA has concerns about whether or not two approved generic versions of Concerta tablets (methylphenidate hydrochloride extended-release tablets), used to treat attention-deficit hyperactivity disorder in adults and children, are therapeutically equivalent to the brand-name drug."[2]

In an apparent confirmation of the FDA's concerns, a case series of children and adolescents with ADHD observed that almost all of the patients showed symptom improvement when they switched from a non-OROS formulation to an OROS preparation at the same dosage.[3]

continued

Clinical Point

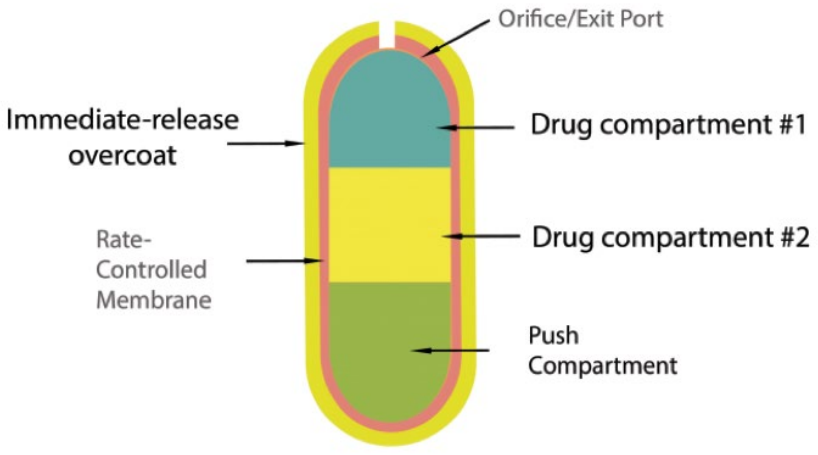
Generic substitution of a brand-name medication can result in worsening of symptoms and increased adverse effects

Clinical Point

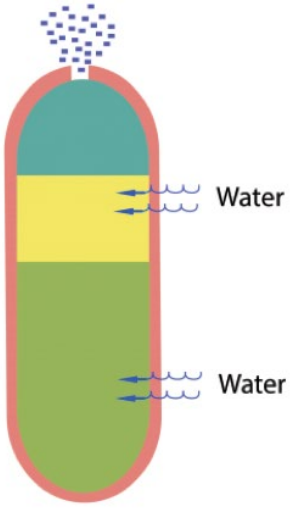
The OROS preparation is thought to provide more predictable medication delivery over an extended period of time

Figure

Osmotic release oral system in Concerta



The outer layer contains an immediate-release methylphenidate. The extended-release portions have 2 drug compartments for even mean plasma concentration of the drug.



Water creates osmotic pressure to activate the push compartment to release methylphenidate from the drug compartments through the orifice in a controlled fashion.

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The OROS preparation is thought to provide more predictable medication delivery over an extended period of time (***Figure***). A patient taking an ER formulation without OROS might lose this benefit, which could lead to symptom destabilization, even if the patient is taking the medication as instructed.

Brand vs generic

Under FDA regulations, companies seeking approval for generic formulations of approved drugs must demonstrate that their products are the same as the brand-name drug in terms of:

- active ingredients
- strength

- dosage form
- route of administration
- packaging label.

In addition, the pharmaceutical company must demonstrate that the generic form is absorbed and distributed to the part of the body at which it has its effect at acceptably similar levels to the brand-name drug. All medications—new or generic, in clinical trials or approved, prescription or over-the-counter—must be manufactured under controlled conditions that assure product quality.

However, some studies have disputed this equivalency. In 1 study, patients with schizophrenia receiving generic olanzapine had lower serum concentration than patients with schizophrenia taking equivalent dosages of brand-name olanzapine.[4] Similarly, studies comparing generic and brand-name venlafaxine showed significant differences in peak plasma concentration (Cmax) between generic and brand-name compounds.[5]

The FDA has considered upgrading the manufacturers' warnings about the risk of generic medications, but has delayed the decision to 2017.[6]

FDA's approval process for generic drugs

To receive approval of a generic formulation in the United States, the FDA requires that the generic drug should be compared with the corresponding brand-name drug in small crossover trials involving at least 24 to 36 healthy volunteers.

Bioequivalence is then established based on assessments of the rate of absorption (Cmax and area under the plasma concentration-time curve [AUC]). The FDA's criteria are designed to achieve 90% confidence that the ratios of the test-to-reference log-transformed mean values for AUC and Cmax are within the interval of 80% to 125%. The FDA accepts −20% to 25% variation in Cmax and AUC in products that are considered bioequivalent. This is much less stringent than its −5% to 5% standard used for brand-name products. The FDA publishes a list of generic drugs that have been certified as bioequivalent, known as the "Orange Book."[5]

Considerations when substituting generic medication

Because of the growing number of generic formulations of the same medication, generic–generic switches are becoming more commonplace. Theoretically, any 2 generic versions of the same medication can have a variation of up to 40% in AUC and Cmax. Generic medications are tested in healthy human controls through single-dose studies, which raises concerns about their applicability to the entire patient population.

Bioequivalence. It is a matter of debate whether bioequivalence translates to therapeutic equivalency. For medications with a narrow therapeutic index, the FDA has accepted that these 2 phenomena are not necessarily linked. With the exception of a few medications, including lithium and some anticonvulsants such as divalproex sodium and carbamazepine, serum level of the medications usually does not predict clinical response.

Inert ingredients. Generic medications can include inert ingredients (excipients) that are different from those in their branded counterparts. Some of these inactive ingredients can cause adverse effects. A study comparing paroxetine mesylate and paroxetine hydrochloride showed differences in bioequivalence and clinical efficacy.[7]

In some cases, brand-to-generic substitution can thwart clinical progress in a stable patient. This small change in the medication could destabilize the patient's condition, which, in turn, may lead to unnecessary and significant social and financial burdens on the patient's family, school, community, and the health care system.

Clinical Point

Theoretically, any 2 generic versions of the same medication can have a variation of up to 40% in AUC and Cmax

continued

Related Resources

- U.S. Food and Drug Administration. Fact sheet: what's involved in reviewing and approving generic drug applications? www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm506040.htm.
- Desmarais JE, Beauclair L, Margolese HC. Switching from brand-name to generic psychotropic medications: a literature review. CNS Neurosci Ther. 2011;17(6):750-760.

Drug Brand Names

Carbamazepine • Tegretol
Divalproex • Depakote
Lithium • Eskalith, Lithobid
Methylphenidate extended-release • Concerta
Olanzapine • Zyprexa
Paroxetine • Paxil

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Prescribers should remain cognizant of drug switches from brand to generic and from one generic to another

Recommendations

In the event of a change in clinical response, clinicians first should evaluate adherence and explore other factors, such as biological, psychological, medical, and social issues. Adherence can be adversely affected by a change in the physical characteristics of the pill. Prescribers should remain cognizant of brand–generic and generic–generic switches. It may be reasonable to adjust the dosage of the new generic medication to address changes in clinical effectiveness.

If these strategies are ineffective, consider switching to a brand-name medication. Write "Dispense As Written" on the prescription to ensure delivery of the branded medication or a specific generic version of the medication.

An insurance company might require prior authorization to approve payment for the brand medication. To save time, use electronic forms or fax for communicating with the insurance company. Adding references to FDA statements and research papers, along with the patient's history and presentations, would be prudent to demonstrate doubts about efficacy of the generic medication.

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Bottom Line

Generic medications can differ in bioequivalence and clinical response from their brand-name or other generic counterparts. When a stable patient shows signs of sudden clinical deterioration, consider a brand–generic switch as a possible factor.