

Seeing snakes that aren't there

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While being treated for ADHD, R, age 9, begins seeing snakes everywhere, hitting others, and throwing objects across the room. How do you proceed?

How would you handle this case?

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CASE Disruptive and inattentive

R, age 9, is brought by his mother to our child/adolescent psychiatry clinic, where he has been receiving treatment for attention-deficit/hyperactivity disorder (ADHD), because he is experiencing visual hallucinations and exhibiting aggressive behavior. R had initially been prescribed (and had been taking) short-acting methylphenidate, 5 mg every morning for weeks. During this time, he responded well to the medication; he had reduced hyperactivity, talked less in class, and was able to give increased attention to his academic work. After 2 weeks, because R did not want to take short-acting methylphenidate in school, we switched him to osmotic-controlled release oral delivery system (OROS) methylphenidate, 18 mg every morning.

Two days after starting the OROS methylphenidate formulation, R develops visual hallucinations and aggressive behavior. His visual hallucinations—which occur both at home and at school—involve seeing snakes circling him. When hallucinating, he hits and pushes family members and throws objects at them. He refuses to go to school because he fears the snakes. The hallucinations continue throughout the day and persist for the next 3 to 4 days.

R does not have any comorbid medical or psychiatric illnesses; however, his father has a history of schizophrenia, polysubstance

abuse, and multiple prior psychiatric hospitalizations due to medication noncompliance.

R undergoes laboratory workup, which includes a complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone level, and urine drug screening. All results are within normal limits.

What should be part of the diagnostic consideration for R's hallucinations?

- a) onset of a new mood or psychotic disorder
- b) delirium
- c) psychosis due to stimulant medication

The authors' observations

We ruled out delirium by ordering a basic laboratory workup. We considered the possibility of a new mood or psychotic disorder, but began to suspect the OROS methylphenidate might be causing R's symptoms.

Attention-deficit/hyperactivity disorder is an increasingly prevalent diagnosis in the United States, affecting up to 6.4 million

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children age 4 to 17. While symptoms of ADHD often first appear in preschool-age children, the average age at which a child receives a diagnosis of ADHD is 7.

Stimulants are a clinically effective treatment for ADHD. In general, their use is safe and well tolerated, especially in pediatric patients. Some common adverse effects of stimulant medications include reduced appetite, headache, and insomnia.¹ Psychotic symptoms such as paranoid delusions, visual hallucinations, auditory hallucinations, and tactile hallucinations are rare. In some cases, these psychotic symptoms can be accompanied by increased aggression.²⁻⁴

Methylphenidate is one of the most commonly prescribed stimulants for treating ADHD. Methylphenidate has 2 known mechanisms of action: 1) inhibition of catecholamine reuptake at the presynaptic dopamine reuptake inhibitor, and 2) binding to and blocking intracellular dopamine transporters, inhibiting both dopamine and norepinephrine reuptake.^{5,6} Because increased levels of synaptic dopamine are implicated in the generation of psychotic symptoms, the pharmacologic mechanism of methylphenidate also implies a potential to induce psychotic symptoms.⁷

How common is this problem?

On the population level, there is no detectable difference in the event rate (incidence) of psychosis in children treated with stimulants or children not taking stimulants.⁸ However, there are reports that individual patients can experience psychosis due to treatment with stimulants as an unusual adverse medication reaction. In 1971, Lucas and Weiss⁹ were among the first to describe 3 cases of methylphenidate-induced psychosis. Since then, many articles in the scientific literature have reported cases of psychosis related to stimulant medications.

A brief review of the literature between 2002 and 2010 revealed 14 cases of

stimulant-related psychosis, in patients ranging from age 7 to 45. Six of the patients were children, age 7 to 12; 1 patient was an adolescent, age 15; 4 were young adults, age 18 to 25; and 3 were older adults. Of all 14 individuals, 7 reported visual hallucinations, 4 had tactile hallucinations, 4 had auditory hallucinations, and 3 displayed paranoid delusions.¹⁰ With the aim of exploring possible etiologic factors associated with psychotic symptoms, such as type of drug and dosage, it was found that 9 patients received methylphenidate, with total daily doses ranging from 7.5 to 74 mg (3 patients received short-acting methylphenidate; 1 patient received methylphenidate extended release (ER); 1 patient received both; 4 patients received dextroamphetamine, with doses of 30 to 50 mg/d; and 1 patient received amphetamine, 10 mg/d). In terms of family history, 1 patient had a positive family history of schizophrenia; 1 patient had a family history of bipolar disorder; and 6 patients were negative for family history of any psychotic disorder.¹⁰

In 2006, due to growing concerns about adverse psychiatric effects of ADHD medications, the FDA Center for Drug Evaluation and Research Office of Surveillance and Epidemiology requested the electronic clinical trial databases of manufacturers of drugs approved for the treatment of ADHD, or those with active clinical development programs for the same indication.¹¹ In that study, Mosholder et al¹¹ analyzed data from 49 randomized, controlled clinical trials that were in pediatric development programs and found that there were psychotic or manic adverse events in 11 individuals in the pooled active drug group. These were observed with methylphenidate, dextromethylphenidate, and atomoxetine. There were no events in the placebo group, which reinforced the causality between the ADHD medication and these symptoms, as participants with untreated ADHD did not develop them.¹¹

Clinical Point

The pharmacologic mechanism of methylphenidate also implies a potential to induce psychotic symptoms

It is important to note that ADHD medications taken in excessive doses are much more likely to provoke psychotic adverse effects than when taken at therapeutic doses. However, as seen in our clinical case, patients such as R could develop acute psychosis even with a lower dosage of stimulant medications. An article by Ross² suggested rates of .25% for this psychiatric adverse effect (1 in 400 children treated with therapeutic doses of stimulants will develop psychosis), which is consistent with the data from the Mosholder et al¹¹ study.

TREATMENT Discontinuation and re-challenge

After 3 days, we discontinue OROS methylphenidate. Five days after discontinuation, R's visual hallucinations and aggressive behaviors completely resolve. After not receiving stimulants for 2 weeks, R is restarted on short-acting methylphenidate, 5 mg/d, because he had a relatively good clinical response to short-acting methylphenidate previously. After 14 days, the short-acting methylphenidate dosage is increased to 5 mg twice daily without the re-emergence of psychosis or aggressive behaviors.

The authors' observations

Although stimulant-induced psychosis can be a disturbing adverse effect, severe ADHD greatly affects a person's functioning at school and at home and can lead to several comorbidities, including depression, anxiety, and substance abuse. For these reasons, most patients with ADHD who experience psychotic symptoms are re-challenged with stimulants.¹⁰ Out of the 14 cases discussed above, 4 patients were restarted on the same stimulant or a different ADHD medication; 2 of them had the same psychotic symptoms days after the reintroduction of the drug and the other 2 had no recurrence.^{10,12,13}

Stimulant-induced hallucinations

The emergence of hallucinations with methylphenidate or amphetamines has been attributed to a chronic increase of dopamine levels in the synaptic cleft, while the pathophysiological mechanisms are not clearly known. In some cases, hallucinations emerged after taking the first low dose, which has been thought to be an effect of idiosyncratic mechanism. Stimulants cause an increase of the releasing of catecholamines. Porfirio et al¹⁴ argue that high-dose stimulants can deteriorate the response to visual stimuli, causing a different perception of visual stimuli in susceptible children, based on the information that norepinephrine is released in the lateral geniculate nucleus, and it increases the transmission of visual information.

An idiosyncratic drug reaction

Despite the existence of many theories on the pathophysiology of stimulant-induced psychosis (*Box*,¹⁵⁻¹⁸ *page 46*), its actual mechanism remains unknown. In R's case, given the speed with which his symptoms developed, the proposed mechanisms of action may not explain his psychotic symptoms. We must consider an idiosyncratic drug reaction as an explanation. This suggestion is supported by the fact that re-challenging with a stimulant did not re-induce psychosis in 2 out of the 4 cases described in the literature,^{10,12,13} as well as in R's case.

Although the mechanisms by which psychotic symptoms associated with stimulants occur remain unknown, possibilities include^{10,19}:

- genetic predisposition
- changes induced by stimulants at the level of neurotransmitters, synapses, and brain circuits
- an idiosyncratic drug reaction.

What to consider before prescribing stimulants

While stimulants are clearly beneficial for the vast majority of children with ADHD,

Clinical Point

Before initiating treatment with stimulants, determine if the patient has a family history of mood or psychotic illnesses

Box

The pathophysiology of stimulant-induced psychosis

Although the subjective effects of methylphenidate and amphetamines are similar, neurochemical effects of the 2 stimulants are distinct, with different mechanisms of action. Methylphenidate targets the dopamine transporter (DAT) and the noradrenaline transporter (NET), inhibiting DA and NA reuptake, and therefore increasing DA and NA levels in the synaptic cleft. Amphetamine targets DAT and NET, inhibiting DA and NA reuptake, and therefore increasing DA and NA levels in the synaptic cleft. It also enters the presynaptic neuron, preventing DA/NA from storing in the vesicles. In addition, it promotes the release of catecholamines from vesicles into the cytosol and ultimately from the cytosol into the synaptic cleft.¹⁸

Generally, amphetamines are twice as potent as methylphenidate. As such, lower doses of amphetamine preparations can cause psychotic symptoms when compared with methamphetamine products.¹⁷ Griffith¹⁵ showed that paranoia manifested itself in all participants who were previously healthy as they underwent repeated administration of 5 to 15 mg of oral dextroamphetamine many times per day for up to 5 days in a row,

leading to cumulative doses ranging from 200 to 800 mg.¹⁵ At such doses, the effects are similar to those obtained with illicit use of methamphetamine, a drug of abuse for which psychosis-inducing effects are well documented.

Psychosis in reaction to therapeutic doses of methylphenidate may have a mechanism of action that is shared by psychosis in response to chronic use of methamphetamine. Several hypotheses have been suggested to explain the mechanism behind stimulant-induced psychosis in cases of chronic methamphetamine use:

- Young,¹⁶ who had one of the first proposed theories in 1981, hypothesized attributing symptoms to dose-related effects at pre- and post-synaptic noradrenergic and dopaminergic receptors.

- Hsieh et al¹⁸ hypothesized that methamphetamine use causes an increased flow of dopamine in the striatum, which leads to excessive glutamate release into the cortex. Excess glutamate in the cortex might, over time, cause damage to cortical interneurons. This damage may dysregulate thalamocortical signals, resulting in psychotic symptoms.¹⁸

Clinical Point

When present, psychotic symptoms may quickly remit upon discontinuation of the medication

there may be a small subgroup of patients for whom stimulants carry increased risk. For example, it is possible that patients with a family history of mood and psychotic disorders may be more vulnerable to stimulant-induced psychotic symptoms that are reversible on discontinuation.²⁰ In our case, R had a first-degree relative (his father) with treatment-refractory schizophrenia.

Attentional dysfunction is a common premorbid presentation for children who later develop schizophrenia or bipolar disorder. Retrospective data from patients with schizophrenia or bipolar disorder document high rates of childhood stimulant use—generally higher even than other groups with attentional dysfunction²¹ and histories of stimulant-associated adverse behavioral effects.²² In these patients, a history of stimulant use is also associated with an earlier age at onset²³ and a more severe

course of illness during hospitalization.²⁴ Stimulant exposure in vulnerable individuals may hasten the onset or worsen the course of bipolar or psychotic illnesses.^{21,25,26}

OUTCOME Well-controlled symptoms

R continues to receive short-acting methylphenidate, 5 mg twice a day. His ADHD symptoms remain well-controlled, and he is able to do well academically.

The authors' observations

Although stimulant-induced psychosis is a rare and unpredictable occurrence, carefully monitoring all patients for any adverse effects of ADHD medication is recommended. When present, psychotic symptoms may quickly remit upon discontinuation of the medication. The question

of subsequently reintroducing stimulant medication for a patient with severe ADHD is complicated. One needs to measure the possible risk of a reoccurrence of the psychotic symptoms against the consequences of untreated ADHD. These consequences include increased risk for academic and occupational failure, depression, anxiety, and substance abuse. Psychosocial interventions for ADHD should be implemented, but for optimal results, they often need to be combined with medication. However, if a stimulant medication is to be reintroduced, this should be done with extreme care. Starting dosages need to be low, and increases should be gradual, with frequent monitoring.

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Related Resource

- Man KK, Coghill D, Chan EW, et al. Methylphenidate and the risk of psychotic disorders and hallucinations in children and adolescents in a large health system. *Transl Psychiatry*. 2016;6(11):e956. doi: 10.1038/tp.2016.216.

Drug Brand Names

Atomoxetine • Strattera	Methylphenidate •
Dexmethylphenidate • Focalin	Metadate, Ritalin
Dextroamphetamine/ amphetamine • Adderall	Methylphenidate ER • Concerta

Clinical Point

Most patients with ADHD who experience psychotic symptoms are re-challenged with stimulants

Bottom Line

Although stimulant-induced psychosis is a rare occurrence, determine if your pediatric patient with attention-deficit/hyperactivity disorder (ADHD) has a family history of mood or psychotic disorders before initiating stimulants. Carefully monitor all patients for any adverse effects of stimulant medications prescribed for ADHD. If psychotic symptoms occur at therapeutic doses, reduce the dose or discontinue the medication. Once the psychotic or manic symptoms resolve, it may be appropriate to re-challenge with a stimulant.

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