Reintroduction of stimulant treatment for patients with ADHD, after stimulant-related psychosis

Practice points

- Clinicians should be aware of possible psychotic side effects with medication treatment of ADHD.
- Psychotic symptoms associated with ADHD medication usually clear with their discontinuation.
- Risks and benefits need to be carefully weighed before considering reintroduction of ADHD medication.
- Reintroduction of ADHD medication needs to be done with very careful monitoring.
- Reintroduction of ADHD medication should start with low dosages that are very slowly increased.

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ADHD is a common condition that affects a large proportion of the child, adolescent and adult population. One of the most widely used medications for treating this illness are psychostimulants, which are generally well tolerated. Nevertheless, one of the rare side effects includes the development of psychotic symptoms. Generally, these symptoms are cleared when the medication is discontinued. There have been several case reports in the literature pertaining to these side effects. Most of them solely involve discontinuation of the medication, but there are four case reports where rechallenging with stimulant medication occurred, with only two of these resulting in recurrence of psychotic symptoms. We report three additional cases where rechallenging with stimulant medication did not result in reappearance of psychotic symptoms. Possible risk factors for developing such side effects and hypothesized mechanisms are discussed.

Keywords: ADHD • psychotic side effects • stimulant medication

ADHD is an increasingly prevalent diagnosis in the USA, affecting up to 4.1 million children in 2007, representing 7.2% of all children aged 4–17 years. Of those, 66.3% were taking medication for the disorder, which consisted in 2.7 million children [1]. Studies show that somewhere between one- and two-thirds of these children should continue to display significant ADHD symptoms into their adult life [2]. Stimulants remain first-line treatment for ADHD, and, like all other psychotropic medications, have a wide range of undesirable side effects, including even psychotic symptoms [3]. These psychotic symptoms range from paranoid delusions to confusion, increased aggression, and, of course, hallucinations, which have been reported to be visual, auditory, tactile and even somatic [4,5]. Lucas and Weiss were among the first to describe three cases of methylphenidate-related hallucinosis in 1971 [6]. Since then, many articles in the scientific literature reported various cases of psychosis related by stimulant medication.

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

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related psychosis, in patients ranging from 7 to 45 years of age. Six of them were children aged 7–12 years old, one of them was an adolescent aged 15, four of them were young adults from 18–25 years old, and three of them were older adults. Of all 14 individuals, seven of these reported visual hallucinations, four had tactile hallucinations, four had auditory hallucinations and three displayed paranoid delusions [3–5,7–11]. While a few developed the symptoms in a few days, others took 1 month to 1 year after the medication was initiated. When it was stopped, resolution of symptoms would generally occur after a few days, although it did take up to a few weeks for one person. With the view of exploring possible etiological factors associated with psychotic symptoms, such as type of drug and dosage, it was found that nine patients were on methylphenidate, with total daily doses ranging from 7.5 to 74 mg (three patients on short-acting Ritalin [Novartis Pharmaceuticals, Surrey, UK], one patient on long-acting Concerta [Janssen Ortho, NJ, USA], one patient on both, and four patients unknown); four patients were on dextroamphetamine, with doses of 30–50 mg daily; and one patient was on amphetamine 10 mg daily. In terms of family history, one patient had a positive family history of bipolar disorder, six had negative family history of any psychotic disorder, and this information is unknown for the other seven patients.

Although stimulant-related psychosis can be a very disturbing side 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, as we see in the literature, some patients are restarted on pharmacological treatment to treat the illness, hoping to avoid a psychotic recurrence. Out of the 14 cases discussed, four were restarted on the same or a different ADHD drug. Two of them had the same psychotic symptoms days after the reintroduction of the drug, but the other two had no recurrence, although the duration of follow-up was not reported [7,8,11]. It is worth noting that psychosocial interventions are at times helpful, even though patients often require the addition of medication for optimal functioning. In the studies mentioned above, it is not clear whether these types of interventions were used and/or whether they were effective.

Owing to growing concerns about psychiatric side effects of ADHD drugs, US FDA Office of Surveillance and Epidemiology conducted in 2006 a comprehensive review of clinical trials on ADHD treatment, as well as postmarketing spontaneous reports. Out of 49 randomized controlled trials that were examined, there were psychotic or manic events in 11 different individuals in the pooled active drug group, which characterized a rate of 1.48 events per 100 person years (representing a sum total of 100 years of treatment). These were observed with methylphenidate, dextromethylphenidate (Focalin; Novartis Pharmaceuticals), atomoxetine (Strattera; Eli Lilly, IN, USA) and modafinil (Alertec; Teva Pharma, Utrecht, The Netherlands). Meanwhile, there was not a single event in the pooled placebo group, in a total of 420 person years, which reinforced the causality between the ADHD medication and such symptoms, as participants with untreated ADHD did not develop them. The mean duration of treatment for the active drug group was 51 days [12].

In the second part of the FDA study, there was a review of 865 unique postmarketing reports from manufacturers of marketed ADHD drugs, between 2000 and 2005, that described cases of psychosis as well as mania. The total sample size is unknown as it was not reported in the study. Out of those 865 different individuals, the majority were from a pediatric population and almost half were 10 years old or younger. They all showed temporal association; 282 of them (32.6%) had a positive dechallenge (resolution of symptoms after the drug is stopped), and nine of them (1.04%) had a positive rechallenge (recurrence of symptoms after the drug is reinstated). It is unclear whether the other ones had a negative rechallenge or no rechallenge at all, but at least one case was observed for each of the six drugs examined (Adderall [Shire, Jersey] [dextroamphetamine-amphetamine], Adderall XR [Shire], Concerta [OROS methylphenidate], Metadate [methylphenidate], Ritalin (methylphenidate) and Strattera [atomoxetine]). This indicates a much greater likelihood that these symptoms are actually true side effects of the medication [12].

It is important to note that ADHD drugs taken in excessive doses are much more likely to provoke psychotic or manic side effects than when taken at therapeutic doses. An article by Ross suggests rates of 0.25% for this psychiatric side effect (one in 400 children treated with therapeutic doses of stimulants will develop psychosis), and this is quite consistent with the data from the FDA study mentioned above [4]. However, high doses of amphetamines can more easily lead to psychotic symptoms such as hallucinations and delusions, which are virtually indistinguishable from schizophrenia. Generally, amphetamines are twice as potent as methylphenidate, thus, much higher dosages of methylphenidate would be needed for such symptoms. One study by Griffith showed that paranoia manifested itself in all subjects, who were previously healthy, as they underwent repeated administration of 5–15 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 [13,14]. At such doses, the effects are similar to those obtained with illicit use of methamphetamines, for which the psychosis-inducing effects are well documented.

In summary, psychosis is a rare side effect of ADHD medication (1.48 events per 100 person years). In most instances, this side effect clears when the medication is discontinued. It is usually not readministered for fear of relapse in hallucinations and paranoia. However, in the very few (only four) reported cases where rechallenging has occurred, there appears to be a 50% recurrence of the psychosis when the drug is restarted. We therefore wish to add to this very sparse literature of three cases of patients with ADHD who developed psychoses after being medicated for ADHD. Their psychotic symptoms cleared upon discontinuation of the medication and did not reoccur upon rechallenging. Factors that may affect the response to rechallenging will be discussed.

Cases

Matthew

Matthew was assessed for his ADHD when he was 6 years old. His growth and development have been normal, and his past medical history was significant for two episodes of pneumonia, at 6 months and 4 years of age. His family history, as reported by his parents, was significant for depression in both parents, and they have both been on Prozac (Eli Lilly) in the past. Several family members on the mother's side also had depression, and one was diagnosed with schizophrenia.

Matthew started to have behavioral problems in kindergarten. In grade 1, loss of focus, short memory span, and forgetfulness were observed in class and at homework time. ADHD and learning deficits with dyslexia were diagnosed, through a careful interview of the patient and his parents, combined with teacher input. In April of his grade 2 year, Concerta 27 mg daily was started. He had better attention and focus in the classroom, he completed homework much more efficiently and his dyslexia improved. Some decrease in concentration was noted over the summer, and Concerta was therefore increased to 36 mg at the beginning of grade 3. The year was uneventful on this higher dose. During the following summer, off Concerta, his previously observed anxiety before treatment had returned and was more severe, as he was described as anxious and "almost paranoid." Concerta was restarted in grade 4 at 36 mg daily. Two months later, he reported still being anxious, and claimed to "see things" that he could not describe with precision: "green blobs" in his peripheral visual fields that seemed to follow him, visible by day or by night, with no auditory component or menace. He admitted having seen similar things the previous summer, off medication. Concerta was discontinued until the winter holiday and restarted thereafter, with no relapse in hallucinations. His academic performance improved and he was off medication over the summer, with fewer mood issues and still no recurrence in psychotic symptoms. He started grade 5 off treatment, but inattention and loss of focus became apparent again, and Concerta was restarted at a lower level – 18 mg daily. He has been on this dosage for 2 months and has reported no hallucinations.

Mary

Mary was first assessed for her ADHD when she was 9 years old. Her past medical history was significant for a fibroblastic reticulum cell tumor, for which she was treated surgically between the ages of 2 to 5. She had no sequelae. However, she had low hemoglobin and was followed by hematology. She also has hyperopic astigmatism. Her perinatal and developmental history are unremarkable. Her family history, as reported by her parents, was positive for schizophrenia in a paternal aunt and attentional difficulties in her mother when she was a child.

Mary's main symptoms that warranted a consultation were attentional difficulties in class, restlessness at home and at school, excessive talking and interrupting others, oppositional attitude with parents and teachers, and general impulsivity. She was carefully assessed by a child psychiatrist and a psychologist, through a detailed psychiatric interview including both parents and herself, as well as a psychological evaluation. She was consequently diagnosed with ADHD, combined type, and a stimulant trial was proposed, in addition to behavioral management. She was therefore started on Biphentin (Purdue Pharma, ON, Canada; methylphenidate CR) 10 mg daily. After 2 weeks, her parents reported a visible improvement, as their daughter was less impulsive, had fewer behavioral issues and had better concentration. She was doing very well at the 1-month follow-up in clinic. However, about 1 week later, 5 weeks into treatment, she acutely developed worrisome psychotic symptoms that warranted a visit to the emergency room. For 2 days, she had been hearing an unrecognizable male voice in class, which kept on telling her she could not do her work. She became paranoid as she felt people were following her, hearing footsteps behind her. She became so scared of the voices that she hid under the desk during class on one instance. In the emergency room, Biphentin was immediately stopped, and she was sent home with close follow-up. Psychotic symptoms have not recurred since then and she was not restarted on medication for a while as her behavior remained somewhat improved. It was only about 16 months later that Biphentin was

restarted, as school and homework were becoming difficult again for Mary. She was doing well on 10 mg, which she took for 5 months, with no relapse in hallucinations or paranoia. It was then gradually increased up to 30 mg within a few months. In the following years, the medication was discontinued and restarted several times because of nonoptimal patient adherence and drug holidays during the summer, but side effects never reappeared. She is now 16 years old and has been taking Biphentin 40 mg daily with short-acting Ritalin 10 mg in the afternoon for the last 11 months, with no major concerns.

John

John consulted for ADHD symptoms at 22 years of age. He reported no significant past medical history and no family history of mental illness. He presented with difficulty focusing in his university classes, and completing assignments, poor organizational skills, poor sense of time, and making careless mistakes. After careful psychiatric and psychological evaluations with the patient alone, and completing a Structured Clinical Interviews for DSM Disorders I and II, he was diagnosed with ADHD and generalized anxiety disorder, mostly related to performance fears and low self-esteem. He started some cognitive–behavioral therapy, and, a few months after his initial assessment, was prescribed Adderall XR 10 mg daily. It was increased to 20 mg 2 weeks later as there was no improvement or side effects. Then, about 6 weeks later, he developed several distressing symptoms over the span of 5 days: light-headedness, nausea, headaches and visual hallucinations. He would see shadows and insects in bright places and specks of light in dark places. Most symptoms resolved spontaneously after 5 days but he still had on and off hallucinations added to some vague paranoia. A week later, in his follow-up appointment, Adderall XR was discontinued gradually in 3 days and he had no clear relapse in psychotic symptoms since then. He admitted being unsure if some things were real or not on a few occasions in the next 2 weeks, but wanted to go back on medication for help with school work. He was therefore started on Biphentin 10 mg daily, approximately 1 month after Adderall XR had been discontinued. He had no side effects after 1 week, and was increased gradually to 30 mg over a few months. He even went up to 40 mg for the last 2 months and still had no relapse in hallucinosis (7 months total on Biphentin).

Discussion

As we can see in our three cases described above, as well as in the literature, stimulant-related psychosis occurs in a wide variety of patients with different ages, symptoms, medications used and length of use. It is, therefore, quite difficult to predict who is at risk of developing psychosis. Even though it is tempting to hypothesize that a family history of psychosis increases the risk of developing psychotic symptoms on stimulant medication, there is no adequate evidence to support this. In fact, out of the total 17 cases reviewed in this article, only three have clear-cut family history of bipolar disorder or psychosis (one in the literature review and two in our own cases). Symptoms appeared on three different drugs (Biphentin, Concerta, and Adderall XR), and they occurred 2–8 weeks after initiation of the drug. The main consistent feature across most cases was the duration of psychotic symptoms, only lasting 2–7 days after discontinuation of the stimulants. This is most probably related to their half-life and is further evidence for direct causality between the medication and the psychotic presentation. However, in Matthew's case, the precipitation of psychotic symptoms due to ADHD medication is less clear-cut, as some vague symptomatology seems to be present off medication. Therefore, the possibility of another diagnosis should be kept in mind.

Several hypotheses have been suggested to explain the mechanism behind stimulant-related psychosis. One of the first proposed theories was by Young in 1981, attributing symptoms to dose-related effects at pre- and post-synaptic noradrenergic and dopaminergic receptors [15]. It has also been hypothesized that if a patient has some psychotic symptoms, which then clear, subsequent environmental stressors or an amphetamine injection can trigger psychotic recurrence. This could be caused by catecholaminergic supersensitivity, as repeated exposure to low doses of amphetamine provides a good model of amphetamine psychosis. Enhanced mesotelencephalic dopamine release upon re-exposure to the drug has been hypothesized as a possible mechanism of action [13]. Another study by Caci *et al.* examines the link between low dopamine β-hydroxylase activity, ADHD and psychosis, through the case of a patient treated with disulfiram developing psychotic symptoms when given the first dose of methylphenidate [16]. Disulfiram effectively blocks dopamine β-hydroxylase, and genetic knockouts of that enzyme are reported to be associated with dopamine supersensitivity [11].

Despite the existence of many theories on the pathophysiology of stimulant-related psychosis, its actual mechanism remains unknown, and the possibility of an idiosyncratic drug reaction is still a possible explanation. This suggestion is supported by the fact that rechallenge with a stimulant did not reinduce psychosis in two out of the four cases described in the literature and the three cases discussed by us [7,8,11]. One was switched from

an amphetamine to methylphenidate, and two were restarted on methylphenidate. The dose of one of these patients was slightly increased after 5 months.

In summary, the mechanisms by which these psychotic symptoms occur in a small number of patients remain undetermined. The possibilities include genetic predisposition, catecholaminergic hypersensitivity and an idiosyncratic drug reaction.

Clinical recommendations

As stimulant-related psychosis is a rare and unpredictable occurrence, careful monitoring of response and side effects to ADHD medication is recommended for all patients. When they are present, psychotic symptoms will quickly remit upon discontinuation of the drug. The question of subsequently reintroducing stimulant medication for the 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 should be tried, but they often need to be combined with medication treatment for optimal results. However, if stimulant medication is to be reintroduced, it needs to be done with extreme care. Beginning dosages need to be low and increases should be gradual, with frequent monitoring. The above recommendations are consistent with the most recent guidelines of the European ADHD Guideline Group [17].

Future perspective

This area requires more careful and systematic research to clarify the possible causes and mechanisms of the development of psychotic symptoms with stimulant treatment. In addition, clinical research that addresses if, when, and how stimulants should be reintroduced, as well as the effects of this rechallenge, needs to be carried out in a systematic and well-controlled fashion. This would provide the guidance clinicians need to appropriately treat this complicated situation, with greater confidence.

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Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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