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.

Psychotic and Manic-like Symptoms During Stimulant Treatment of Attention Deficit Hyperactivity Disorder

Randal G. Ross, M.D.

A boy 6 years 9 months of age was brought by his mother to a child psychiatrist for difficulties with sustained attention, distraction, careless errors, poor listening, difficulty following instructions, difficulty with organization, frequently misplaced items, and forgetfulness in daily activities. He had no history of impulsive or hyperactive behavior, mood symptoms, or tics. He had been born after an unremarkable full-term pregnancy to a 43-year-old mother who did not use alcohol or drugs during pregnancy. The child was delivered by cesarean section after failure to progress in labor and had a normal postnatal course. His family history was negative for mood disorders, psychosis, obsessive-compulsive symptoms, or tics.

Several months later, the symptoms had been confirmed in the home, school, and tutoring environments. The patient, then 7 years 4 months of age, was started on methylphenidate, and he showed a clear dose-response effect. An extended-release formulation of methylphenidate was then prescribed, and the dose was gradually increased over a 2-month period to 40 mg per day. At this dose, the patient had a strongly beneficial response, and the only side effect noted was mild anorexia. Eight months later, at 8 years 3 months of age, after a flu-like illness, he developed new symptoms, which included complaints of hearing voices and seeing "adults" when no one was present, a desire to "throw himself down the stairs," high levels of anxiety, tearfulness at school, an unwillingness to leave his mother's side, and irritability.

Stimulants—particularly methylphenidate and amphetamines—are a critical first-line option in the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents (1). The potential for stimulants to induce psychosis-like or manic-like symptoms in children has been known for at least 35 years, since Lucas and Weiss (2) reported on three cases of "methylphenidate hallucinosis." The terms "hallucinosis" and "toxicosis" are often used to distinguish the transient symptoms associated with stimulant use from the longer-lasting symptoms of schizophrenia and bipolar disorder. The U.S. Food and Drug Administration (FDA), while assessing the significance of rare risks in ADHD treatments, recently asked its Pediatric Advisory Committee to review reports of stimulant-associated psychotic-like and manic-like symptoms. The committee was to comment on the import of the relationship between therapeutic uses of stimulants and psychosis or mania; whether the benefits of stimulants justify a risk of psychosis or mania; and whether information about risk was adequately relayed to the public (3). This case raises the clinical issues of diagnosis and treatment of psychotic-like and manic-like symptoms arising during stimulant use in children with ADHD.

Stimulant-Induced Psychosis or Mania

Stimulant medications at high doses can induce symptoms of mania and psychosis that are highly similar to those of bipolar or schizophrenic illnesses (4, 5). These symptoms generally resolve within 2 days after discontinuation of the stimulant, although symptoms lasting 6 days or longer have been reported (5). The pharmacologic effects of stimulants include the ability to increase dopaminergic and noradrenergic neurotransmission. Observations of clinical similarities between schizophrenia and stimulant-induced psychosis provided initial evidence supporting the dopaminergic theory of schizophrenia (6), and more recent observations suggest that the psychosis seen in methamphetamine abusers reflects an interaction between substance abuse and an underlying vulnerability to psychosis (7). Thus, symptoms induced by high doses of stimulants may provide a window into understanding some forms of psychosis and mania.

Therapeutic Doses of Stimulants

Anecdotal reports (8) have been published on the relation between therapeutic doses of stimulants and mania or psychosis, but the topic has not been closely examined. Recently, the FDA reviewed several pharmaceutical com-

pany-sponsored trials of methylphenidate formulations, amphetamine salts, modafinil, and atomoxetine (9–12). Combining across stimulant medications, during double-blind, placebo-controlled trials, placebo was not associated with any toxicosis events in 3,990 subjects with a combined duration of treatment of over 425 years. For therapeutic doses of active medication, there were 13 reports of toxicosis in 5,717 subjects with a combined treatment duration of over 800 years. In open-label trials, stimulants were associated with 45 reports of toxicosis in 15,999 subjects with a combined treatment duration of almost 9,400 years. Although there are methodological problems in summing across stimulant medications and across studies that may have different sensitivities for identifying psychotic-like and manic-like symptoms, these numbers suggest as a preliminary estimate that toxicosis will occur in approximately 0.25% of children treated with stimulants, or about 1 in 400—a proportion suggesting an infrequent but not rare effect of therapeutic dosing.

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The severity and duration of stimulant-induced toxicosis were also examined. In the FDA studies, a broad array of search terms was used to identify cases of possible toxicosis in pharmaceutical company-sponsored trials. Although this approach is highly sensitive in identifying cases of toxicosis, it also identifies cases with less specific and less severe symptoms, such as anxiety, social withdrawal, aggression, and irritability. When all of these cases were considered as a group of "psychiatric adverse events," the most common outcomes were listed as "not reported" or "not available." Thus, while the FDA reported that, depending on the stimulant, 33%–58% of cases of stimulant-induced "psychiatric adverse events" resolved with discontinuation of the drug, the use of broad search criteria and the lack of outcome data make these numbers difficult to interpret.

An alternative approach to examining adverse outcome data was used in a contribution (13) to the recent national discussion on the relationship between antidepressants and suicidal thoughts. Individually identified cases in the FDA database were subjected to expert review, focusing on particularly clear cases. In an attempt to follow this approach, I examined case reports from FDA publications (9–12) and the literature (2, 14–20) in which descriptive summaries were presented of psychotic-like or manic-like symptoms occurring during stimulant treatment, in which stimulant treatment was discontinued or reduced, and in which outcome was discussed. Data were available for 60 cases. In 55 cases (92%), the psychotic-like or mania-like symptoms resolved, and hence these cases might be better termed stimulant toxicosis than psychosis or mania. In the remaining five cases (8%), psychotic symptoms either continued or recurred after discontinuation of the stimulant; all five of these patients were rediagnosed as having either bipolar disorder or schizophrenia.

Predicting who is at risk of stimulant toxicosis is problematic. The case reports are notable for a broad range in patients' ages (2–17 years), a variety of medications, a wide range for duration of exposure, the symptoms reported, and symptom severity. The cases are similar only in the generally brief duration of stimulant-induced symptoms: recovery typically occurs within 2 days—and almost always within 7 days—of discontinuing the medication or lowering the dose. Moreover, with discontinuation of the stimulant, the reemergence of ADHD symptoms is typically rapid. Family history is unlikely to be a useful clinical predictor. Even among children with a first-degree relative with schizophrenia or bipolar disorder, attentional dysfunction without later onset of psychosis or mania is more common than attentional dysfunction preceding psychosis or mania (21, 22). Moreover, children with the more common forms of pediatric bipolar disorder may benefit from stimulant medication (23). In short, stimulant-induced toxicosis appears to be truly idiosyncratic—an important but infrequent and unpredictable side effect of stimulant treatment.

A Marker of Vulnerability

Most cases of stimulant toxicosis resolve with discontinuation of the stimulant. However, attentional dysfunction, whether measured by cognitive testing (24) or by ADHD-like clinical symptoms (25), is a common premorbid presentation for children who later manifest schizophrenia or bipolar disorder. Retrospective data from patients with schizophrenia or bipolar disorders document high rates of childhood stimulant use—generally higher even than other groups with attentional dysfunction (26) and histories of stimulant-associated adverse behavioral effects (27). In these patients, a history of stimulant use is also associated with an earlier age at onset (28) and a more severe course of illness during hospitalization (29). Stimulant exposure in vulnerable individuals may hasten the onset or worsen the course of bipolar or schizophrenic illnesses (26, 30). Thus, while stimulants are clearly beneficial for the vast majority of children with ADHD, there may be a small subgroup for whom the medications worsen the long-term course of other illnesses. Research aimed at determining whether such a subgroup exists and how to identify it is warranted.

Recommendations

Stimulants are highly beneficial for children with ADHD and are a valuable component of the treatment armamentarium. However, therapeutic doses of stimulants can cause manic-like or psychotic-like symptoms in a small

proportion of treated children. These symptoms can include euphoria, grandiosity, paranoid delusions, confusion, hallucinations, and increased aggression. Other than a history of sustained psychosis or clear sustained mania, there are no good predictors of such responses. The symptoms can occur with the first dose or after months of stable treatment. Thus, caregivers need to be educated about such side effects. The majority of manic-like and psychotic-like reactions present no immediate danger. However, when stimulant toxicosis is identified, patients must be evaluated for symptoms that increase the risk of immediate harm. These include suicidal ideation, command hallucinations, increased aggressive urges, and impaired judgment. If symptoms are not severe or the child is young, increased or continuous direct parental supervision is indicated; if symptoms are severe and the child is older, urgent or emergent evaluation by an experienced mental health professional is warranted. Discontinuation of the stimulant during the acute toxicosis is generally the best approach. After discontinuation of the stimulant, stimulant toxicosis generally resolves within 24–48 hours and almost always within 7 days. Currently, there is no strong evidence that stimulant toxicosis predicts later risk of bipolar or schizophrenic illnesses, and antipsychotic and mood-stabilizing medications have significant side effects. Thus, sustained antipsychotic or mood stabilizer treatment of a child based solely on a history of stimulant toxicosis is generally not warranted. Once the acute psychotic-like or manic-like symptoms resolve, the discontinuation of stimulants is almost always associated with a return of the symptoms that led to stimulant treatments. At that point, treatment strategies often must be reconsidered. Given the highly beneficial effects of stimulants for many patients with ADHD (31), even in cases in which inattention is the primary symptom (32, 33), rechallenge with a stimulant medication is often appropriate, although close follow-up to assess for any return of stimulant toxicosis is indicated. The majority of children who experience brief psychotic-like or manic-like symptoms when taking therapeutic doses of a stimulant will not develop a recurrent psychotic illness, although evaluation for comorbid or premorbid symptoms by clinicians with experience in treating mania or psychosis in young children is appropriate.

For this patient, the dose of methylphenidate was reduced to 20 mg per day, and over the following 3 weeks the psychotic-like symptoms gradually resolved. Several months later, at 9 years 0 months of age, again after a flu-like illness, he developed a milder version of the same symptoms. During this episode, methylphenidate was discontinued, and all symptoms resolved within 36 hours. Methylphenidate was reintroduced 1 week later, and the symptoms did not recur. The patient, now 11 years 4 months of age, has been maintained on methylphenidate since that time. His attentional dysfunction remains markedly reduced, and the psychotic-like symptoms have not recurred.

Received April 8, 2006; revision received April 18, 2006; accepted April 24, 2006. From the Department of Psychiatry, University of Colorado at Denver and Health Sciences Center, Denver. Address correspondence and reprint requests to Dr. Ross, Department of Psychiatry, Box C268-31, 4200 E. 9th Ave., Denver, CO 80262; randy.ross@uchsc.edu (e-mail).

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