

New warnings on stimulants for ADHD: Cause for alarm?

In August the FDA called for new warnings on stimulants used for attention-deficit/hyperactivity disorder (ADHD). Amphetamines now carry black box warnings that say, “Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events.” Amphetamines and methylphenidates used for ADHD include expanded information about cardiovascular risks at usual dosages for patients with heart conditions.

To examine the clinical implications of these warnings, CURRENT PSYCHIATRY hosted a conversation between ADHD experts Anthony Rostain, MD, MA, and Lenard Adler, MD.

Dr. Rostain: Changes to warnings on ADHD medications have many psychiatrists looking for guidance on using stimulants. Can you give us some background and discuss the labeling changes?

Dr. Adler: Stimulants have been used for more than 40 years as ADHD treatments, and they’ve been shown to be highly effective. The FDA, which monitors issues of cardiovascular safety and stimulants in an ongoing way, examined specific isolated cases and changed some of the warnings as a result.

Dr. Rostain: What should practicing psychiatrists be concerned about if they’re thinking of prescribing stimulants for an ADHD patient?

Dr. Adler: The take-home point is that stimulants—because of the way they work—have been known to have minor effects of increasing blood pressure and pulse (*Box 1, page 56*).¹⁻³ Clinicians have known



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about issues regarding stimulant use by patients with pre-existing cardiovascular conditions, but now the warnings are more formal for the methylphenidate and amphetamine products.

Dr. Rostain: An FDA committee recommended black box warnings on all stimulants used for ADHD, but the FDA decided instead to clarify warnings in prescription information for some medications. What was the FDA process?

Dr. Adler: The discussion was internal at the FDA, so I can’t say what their thinking was. The black box warning on amphetamines notes two issues. One is the potential for abuse and diversion, and the other warns of potential for sudden death and serious cardiovascular effects if the drug is misused. A warning has also been placed on all

Box 1

Cardiovascular effects of ADHD medications in healthy children and adults

Researchers at Massachusetts General Hospital have examined the effects of ADHD medications on blood pressure and heart rate in children and adults.

Children and adolescents. The first study¹ was a 1-year extension of an open-label trial of once-daily, osmotic-release methylphenidate (MPH) in 432 children (age 6 to 13) with ADHD. Their blood pressure and heart rate were recorded at baseline and monthly.

At 12 months, MPH use at 18 to 54 mg/d was associated with minor but statistically significant mean increases in:

- systolic blood pressure (3.3 mm Hg [$P < 0.001$])
- diastolic blood pressure (1.5 mm Hg [$P < 0.001$])
- heart rate (3.9 bpm [$P < 0.0001$]).

Adults. In a 24-month study,² 223 healthy adults with ADHD (age ≥ 18) received mixed amphetamine salts extended-release (MAS XR) in an open-label extension of a 4-week, double-blind, placebo-controlled trial. MAS XR was started at 20 mg/d for 1 week, then increased up to 60 mg/d based on therapeutic effect, as measured by the ADHD Rating Scale IV.

Blood pressure and pulse were measured at baseline, weekly, then monthly, and 12-lead ECGs were obtained at baseline, weekly, then at 3- and 6-month intervals. Changes after 2 years were small and not statistically significant:

- systolic blood pressure (2.3 ± 12.5 mm Hg)
- diastolic blood pressure (1.3 ± 9.2 mm Hg)
- pulse (2.1 ± 13.4 bpm).

A clinically insignificant increase was observed in the mean QTcB interval (7.2 msec; $P < 0.001$), although no patient's QTcB interval exceeded 480

msec. Seven patients dropped out because of cardiovascular side effects (5 with hypertension, and 2 with palpitation/tachycardia), which were not reported as being serious.

Stimulants and nonstimulants. In another study,³ the same researchers analyzed the cardiovascular effects of three stimulants (methylphenidate, amphetamine compounds, and pemoline) and two nonstimulants (bupropion and desipramine) used to treat ADHD in adults. Data on a total of 125 patients (mean age 39 ± 9 years) from three previous placebo-controlled studies were re-examined for the medications' effects on blood pressure and heart rate.

Minor but statistically significant changes in blood pressure and heart rate were found to be associated with both stimulant and nonstimulant medications:

- systolic blood pressure (bupropion, +5.9 mm Hg [$P < 0.05$]; amphetamine, +5.4 mm Hg [$P < 0.05$])
- diastolic blood pressure (desipramine, +7.1 mm Hg [$P < 0.05$])
- heart rate (bupropion, +6.9 bpm [$P < 0.05$]; amphetamine, +7.3 bpm [$P < 0.05$]; methylphenidate, +4.5 bpm [$P < 0.05$]).

In the last two studies, the authors concluded that although the cardiovascular effects of ADHD medications in healthy adults were minimal, clinicians should monitor vital signs at baseline and periodically during treatment.

methylphenidate products regarding cardiovascular risk for patients with pre-existing cardiovascular conditions, but it is not a black box warning.

Dr. Rostain: How were the warnings clarified?

Dr. Adler: The FDA has changed the language. Now physicians are warned that sudden death can occur at usual doses in patients with a pre-existing structural cardiac abnormality or other serious heart problem. So, stimulants generally should not

be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Dr. Rostain: What about adults?

Dr. Adler: The language is the same for adults. Adults have a greater likelihood than children of

having a history of serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other cardiac problems. Adults with such abnormalities generally should not be treated with stimulant drugs.

Dr. Rostain: What's the impact for clinicians?

Dr. Adler: Clinicians have known that stimulants should not be used in patients with significant pre-existing cardiovascular conditions. That generally includes structural abnormalities such as serious heart murmurs and abnormalities of the electroconduction of the impulse through the heart. When patients present with a history of cardiac abnormalities, clinicians should speak to the pediatrician, primary care physician (PCP), or cardiologist, go over the risk factors, and decide whether these medications can be prescribed for the patient.

Dr. Rostain: Should psychiatrists perform screening tests before prescribing stimulants? When should they consult with a specialist?

Dr. Adler: There is no recommendation in the prescribing information. But clearly a clinician should determine whether a patient has structural cardiac abnormalities or serious heart problems. That means taking a history about heart murmur, syncope, or other serious heart problems. Also, you want to know if the patient is hypertensive. The burden is on the prescribing clinician.

Dr. Rostain: Suppose you have a patient with hypertension or a history of a heart condition, should that patient first be evaluated by a cardiologist? What about a screening ECG?

Dr. Adler: There are no specific recommendations. If clinicians have questions about prescribing the medication, they should consult with the patient's PCP or cardiologist.

Dr. Rostain: Let's say the patient has some heart issues, but the PCP or pediatrician gives the go-

ahead to prescribe stimulants. What sort of monitoring do you recommend?

Dr. Adler: I can't answer that directly. Clearly, you're going to want to partner with the PCP to establish a plan of how to carefully monitor this patient. FDA guidelines recommend ongoing blood pressure monitoring, especially if the patient is hypertensive, but do not specify how often.

Dr. Rostain: What alternatives do psychiatrists have when treating ADHD in patients in whom stimulants may pose some risk?

Dr. Adler: The only approved nonstimulant ADHD medication is atomoxetine, the labeling of which carries language about possible effects on blood pressure. The

FDA warning about structural cardiac abnormalities has not been extended to atomoxetine, but blood pressure needs to be monitored. Whether our medical colleagues feel comfortable using a nonstimulant in patients with structural cardiac abnormalities has not been determined.

Dr. Rostain: In the absence of guidelines in the new warnings on stimulants, are there any studies to help clinicians with treatment and monitoring?

Dr. Adler: There's very little data. A group at Massachusetts General Hospital has been studying the effects of ADHD medication on adults with hypertension (*Box 2, page 58*).⁴ That's a different issue than a structural cardiac abnormality, but at least we have some data. This group found that you can safely give stimulants to hypertensive patients by partnering with medical colleagues and monitoring the patient carefully. Antihypertensive dosages may need to be adjusted during psychostimulant treatment.

Dr. Rostain: How do you choose a medication if your patient has a structural heart abnormality?

Dr. Adler: Again, we don't have a lot of data. The decision would depend on the cardiac abnormality

Establish a plan with the primary care physician to carefully monitor patients with heart condi-

Box 2

Preliminary data: Stimulants' effects on adults with hypertension

In a short-term, open-label trial by Wilens et al,⁴ 13 adults with ADHD and hypertension received mixed amphetamine salts extended-release (MAS-XR), up to 60 mg/d, for 6 weeks (phase 1), then discontinued MAS-XR for 2 weeks (phase 2). All patients had normal blood pressure (<135/85 mm Hg) for at least 4 weeks before entering the study and received a comprehensive clinical assessment, including ECG. Blood pressure was measured manually at each clinic visit.

Single episodes of hypertension (>140/90 mm Hg) occurred at similar rates in each phase, but these episodes were not sustained at any two consecutive visits. Group mean systolic and diastolic blood pressures and pulse did not increase during stimulant treatment. No clinically significant ECG changes were observed, and no serious adverse events occurred.

The authors concluded that this preliminary trial suggests that adults with ADHD and controlled hypertension can be safely treated with stimulant medications.

and the consulting physician's comfort level. Keep in mind that psychostimulants have a short duration of effect, so the effects of the medication can dissipate fairly quickly. Again, the decision to medicate a patient with pre-existing cardiac abnormalities must be done with medical guidance.

Dr. Rostain: So are you saying clinicians should make decisions about prescribing stimulants for patients with ADHD on a case-by-case basis?

Dr. Adler: Exactly.

Dr. Rostain: What about children and adolescents who have unknown structural heart defects? A lot of parents are concerned about reports of sudden cardiac death in young athletes, such as when

playing soccer or basketball. Is there any way for practitioners to protect children with ADHD from an unexpected event?

Dr. Adler: In general, stimulants are safe medications, but we don't have guidelines to help us determine who will need an ECG and who will not. Children are less likely to have had an ECG in the past than an adult, so it's important to do a history, obtain input from the pediatrician or PCP, and clearly review the risks and benefits of medication therapy with the patient's family.

Dr. Rostain: What would you advise clinicians to tell parents of children with ADHD or adult patients who have concerns about the new labeling on stimulants?

Dr. Adler: It would be a shame if patients were not receiving treatment for ADHD because of unfounded medical concerns. When these medications are used appropriately, they have dramatic and positive effects on ADHD.

ADHD is common and highly impairing. Deciding not to treat it has serious consequences in terms of divorce, separation, underperformance in school and on the job, unemployment, smoking, substance use, and issues with motor vehicle accidents and driving.

The goal of treatment is for our patients to get better, and ADHD is highly treatable with medication. But we must be cognizant of the warnings and prescribe medications appropriately. The message is that we've got to work collaboratively with our partners in medicine and, in the absence of guidelines, use good common sense.

References

1. Wilens TE, Biederman J, Lerner M; Concerta Study Group. Effects of once-daily osmotic-release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder: results from a one-year follow-up study. *J Clin Psychopharmacol* 2004;24(1):36-41.
2. Biederman J, Spencer TJ, Wilens TE, et al. Long-term safety and effectiveness of mixed amphetamine salts extended release in adults with ADHD. *CNS Spectr* 2005;10(12 suppl 20):16-25.
3. Wilens TE, Hammerness PG, Biederman J, et al. Blood pressure changes associated with medication treatment of adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2005;66(2):253-9.

 **Related resources**

- ▶ Wilens TE, Hammerness PG, Biederman J, et al. Blood pressure changes associated with medication treatment of adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2005;66:253-9.

DRUG BRAND NAMES

Atomoxetine • Strattera
Bupropion • Wellbutrin
Desipramine • Norpramin

Methylphenidate • Concerta, Ritalin
Mixed amphetamine salts • Adderall
Pemoline • Cylert

DISCLOSURES

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Dr. Rostain is a consultant to Shire and a speaker for Eli Lilly and Company and Ortho-McNeil.

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- 4. Wilens TE, Zusman RM, Hammerness PG, et al. An open-label study of the tolerability of mixed amphetamine salts in adults with attention-deficit/ hyperactivity disorder and treated primary essential hypertension. *J Clin Psychiatry* 2006;67(5):696-702.