

# Heart Rate Changes After Stimulants Negligible

BY DAMIAN McNAMARA

FROM A MEETING OF THE NEW CLINICAL DRUG EVALUATION UNIT

BOCA RATON, FLA. – The use of methylphenidate or mixed amphetamine salts for attention-deficit/hyperactivity disorder can increase heart rate, blood pressure, and the QT interval in children, adolescents, and adults, according to a review of placebo-controlled and open-label extension trials published since 2000.

The magnitude of the effects appears small for most patients, which points to the importance of screening for preexisting cardiovascular disease and asking about any relevant family or patient history, Dr. Raul R. Silva said.

Despite long-term use and the effectiveness of these stimulant medications to reduce core symptoms of ADHD, concerns arose about increased potential for cardiovascular events. The American Heart Association released guidelines for cardiac monitoring of all children with ADHD before treatment (*Circulation* 2008;117:2407-23). “Some of what they came out with was severe,” said Dr. Silva, vice chair of the department of child and adolescent psychiatry at New York University. For example, he pointed out, the American Academy of Pediatrics said it had to temper its recommendations (*Pediatrics* 2008;122:451-3).

Ultimately, the two organizations released a clarification statement that recognizes the need for responsible cardiovascular monitoring while not withholding these medications to treat ADHD, Dr. Silva said (*J. Dev. Behav. Pe-*

*diatr.* 2008;29:335). Despite the joint clarification, confusion about the actual risks remains, Dr. Silva said.

To determine more, Dr. Silva and his colleagues identified and reviewed five double-blind, placebo-controlled studies and six open-label studies that reported relevant cardiovascular data.

“We looked at 10 years’ worth of studies in children and adults that reported heart rate, blood pressure, and EKG changes,” Dr. Silva said in an interview at his poster presentation during the meeting, which was sponsored by the



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DR. SILVA

National Institute of Mental Health.

Both types of studies were included because double-blind, placebo-controlled studies “are so short, there is not always a clear picture” and because “long-term studies tend to be open label,” said Dr. Silva, who also has a private practice in Cresskill, N.J.

In the double-blind studies, mean heart rate increased by 1-8.5 beats per minute after 3-6 weeks of treatment. The percentages of patients who experienced predefined, “clinically notable” heart rate events were similar among groups who received methylphenidate

(MPH), mixed amphetamine salts (MAS), or placebo. Significant increases of 1.5-4.4 bpm in mean heart rate were reported by most of the long-term, open-label extension studies. A comparison of the short-term and long-term studies does not suggest an accumulative risk, Dr. Silva said. He added that it is unclear whether long-term increases in heart rate associated with these stimulants could increase the risk for stroke, heart attacks, or dysrhythmias.

“It may be reasonable to assume that increases in heart rate with therapeutic doses of stimulants are relatively safe in patients without predisposing or preexisting cardiac risk factors; however, further research and data are required to confirm any potential increased risk for cardiovascular events later in life,” the authors wrote.

In terms of blood pressure changes, most of the double-blind studies demonstrated no significant increases with stimulant treatment, compared with baseline. Again, the percentages of patients who experienced clinically notable increases in blood pressure were similar among groups that received MPH, MAS, or placebo.

In contrast, most of the open-label studies found significant increases in systolic blood pressure (0.6-3.5 mm Hg) and diastolic blood pressure (0.7-2.6 mm Hg), compared with baseline. Despite the disparity in significance, numerically, the changes in blood pressure in both study types were similar, suggesting no accumulative effect.

Researchers have not demonstrated a relationship between such small increas-

es in blood pressure and increased morbidity, Dr. Silva said. It is also unclear whether these increases translate to an increased risk for cardiovascular events in patients with preexisting hypertension.

“In essence, you end up seeing [that] there aren’t that many serious changes that occur, and there are some you see in the placebo group as well,” Dr. Silva said. Even so, he added, the rate for these heart rate and blood pressure changes “tends to be a little higher for stimulant drugs, and that is what you want to be most concerned about.”

Acute consequences in children with preexisting cardiac disease and the unknown potential for long-term adverse effects in all children who are exposed to these stimulants are two major concerns. “Personally, I always follow up [with patients]. I take a family history, for example, of arrhythmias, and personal history for syncope and chest pain,” Dr. Silva said.

These are among the recommendations in the 12-item screening recommendations from the American Heart Association (*Circulation* 2008;117:2407-23 and *Circulation* 2007;115:1643-55). Also, pay attention to symptoms such as palpitations, near syncope, or syncope that could indicate a cardiac condition. Family history should include hypertrophic cardiomyopathy, long QT syndrome, Wolff-Parkinson-White syndrome, and Marfan syndrome.

Novartis Pharmaceuticals Corp. supported the study. Dr. Silva disclosed that he is a consultant and on the speakers bureau for Novartis. ■

## ADHD Diagnoses ‘Extremely Transient’ Over 1-Year Period

BY MITCHEL L. ZOLER

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY

NEW YORK – A diagnosis of attention-deficit/hyperactivity disorder might not be forever.

In fact, it can be pretty fleeting. Analysis of serial assessments of more than 8,000 U.S. children and adolescents for attention-deficit/hyperactivity disorder (ADHD) showed that the diagnosis often did not persist after follow-up of 1 year or longer, J. Blake Turner, Ph.D., said at the meeting.

ADHD diagnoses “are extremely transient over a 1-year period. Generally, loss of the diagnosis is more likely than persistence,” said Dr. Turner, a researcher in the division of child and adolescent psychiatry at Columbia University in New York.

The findings suggest that problems exist with current nosology for ADHD, and that current prevalence estimates from community studies may be inflated. “We need to examine the predictors of ADHD persistence over time,” he said. “We need to look at what’s going on here and what predicts the persistence of disruptive disorders.

“If patients are diagnosed with ADHD and it is transient – if it is reactive distress that is likely to go away – do we want to identify them?” he asked in an interview. “If a diagnosis is made of ADHD, do you let it go because it will likely resolve on its own, or will treatment help it resolve more quickly?” We think of ADHD as something that lasts, not something that comes and goes.

Perhaps we need [a diagnosis] that’s more stable,” possibly by basing it on a larger number of symptoms. “That would mean changing the ADHD diagnosis,” he said.

Preliminary analysis of serial assessments for oppositional defiance disorder and conduct disorder in the same data set of 8,714 children and adolescents showed similar, transient patterns after an initial diagnosis, Dr. Turner added.

“It troubles me that the [ADHD] phenotype looks so unstable,” commented Dr. Daniel S. Pine, chief of the Section on Development and Affective Neuroscience at the National Institute of Mental Health. “A lot of people are struggling with the threshold for [diagnosing] ADHD. This is a very different conceptualization of ADHD; we don’t usually think of it as something that’s gone in 2 years. If this is [children having] a transient reaction to stress, I don’t want to talk about it [in] the same way as clinical ADHD.

Dr. Pine suggested that Dr. Turner’s new finding might help explain the high reported prevalence rates of ADHD, and that the results also raised issues about using stimulants to treat newly diagnosed ADHD.

“I look at some of the prevalences [reported], and it’s absurd. I find it very hard to believe that 20% of American boys have ADHD,” but that is what some recent reports documented, Dr. Pine said. Other reports said that about 6% of all American children and about 12% of boys receive stimulant treatment for ADHD. “When I look at these data [in Dr. Turner’s report], the question of stimulant use is right behind there.”

Dr. Turner used data collected by 4 of the 16 studies

done by researchers in the DISC (Diagnostic Interview Schedule for Children) Nosology Group. All of the studies used the DISC to assess a group of children, adolescents, or both. The four studies used by Dr. Turner included serial assessments using the DISC for ADHD a year or more apart. Depending on the study and whether the diagnostic criteria included the age of onset, the range of ADHD prevalence at the initial examination was 5%-40%, with roughly 1,200 total cases identified.

At a follow-up visit at least 1 year after the initial examination, loss of the ADHD diagnosis occurred in roughly 55%-75% of the patients who had been diagnosed with inattention ADHD the first time. In patients who were initially diagnosed with hyperactive ADHD, the loss rate at follow-up ran 55%-65%. Those who were first diagnosed with combined ADHD had a more stable course, with about 18%-35% not maintaining the diagnosis at follow-up.

Additional analysis showed that lost ADHD diagnoses usually did not occur as a small change in an initially marginal diagnosis. Patients who changed from having ADHD to not having it lost five ADHD symptoms, on average. And the remitters and nonremitters all had a similar pattern of disease severity at their initial diagnosis. Patients’ age had no association with whether or not an ADHD diagnosis disappeared. And patients who received treatment had a higher likelihood of retaining their ADHD diagnosis at follow-up than did those who did not receive treatment, possibly because the patients who were treated generally had more chronic ADHD.

Dr. Turner had no disclosures. ■