PEDIATRIC NEUROLOGY BRIEFS
A MONTHLY JOURNAL REVIEW

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Vol. 25, No. 12 December 2011

ATTENTION DEFICIT DISORDERS

CARDIOVASCULAR EVENTS AND STIMULANTS FOR ADHD

Researchers from Vanderbilt University, TN; Kaiser Permanente, California; and other centers conducted a retrospective cohort study of serious cardiovascular events in 1,200,438 children and young adults, ages 2 to 24 years (mean 11.1 years), with ADHD. Automated data from four health plans in North America (Tennessee and Washington State Medicaid, Kaiser Permanente California, and OptumInsite Epidemiology) included records of filled prescriptions. Criteria for inclusion were as follows: use of an ADHD drug (methylphenidate, dexmethylphenidate, dextroamphetamines, amphetamine salts, atomoxetine, or pemoline); an age of 2 to 24 years on the first day of use; continuous drug benefits for 365 days before the first day of qualifying use; and absence of life-threatening serious illness. Patients with congenital heart disease were included. Exclusion criteria included a hospital discharge for acute myocardial infarction or stroke during the preceding 365 days. Two nonuser control subjects were randomly selected for each patient receiving an ADHD medication. The primary study endpoint was a serious cardiovasculr event, defined as sudden cardiac death, myocardial infarction, or stroke persisting >24 hours. Mean length of follow-up was 2.1 years. Current users were more likely to have asthma, seizures, and congenital heart defects.

A total of 81 cohort members had a serious cardiovascular event, or 3.1 per 100,000 person-years, including 33 sudden cardiac deaths (1.3 per 100,000 person–years), 9 acute myocardial infarctions, and 39 strokes. Older age, use of antipsychotic drug, major psychiatric illness, a serious cardiovascular condition, and chronic illness were associated with increased risk of serious cardiovascular event. Compared with nonusers, current use of an ADHD drug was not associated with a significantly increased risk of serious cardiovascular events (hazard ratio, 0.75: 95% confidence interval, 0.31 to 1.85). However, the upper limit of the 95% confidence interval suggested that a doubling of the risk compared to nonusers could not be ruled out. (Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults.

PEDIATRIC NEUROLOGY BRIEFS (ISSN 1043-3155) © 2011 covers selected articles from the world literature and is published monthly The editor is Pediatric Neurologist at Children's Memorial Hospital; Professor Emeritus, Northwestern University Medical School, Chicago, IL.
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N Engl J Med Nov 1, 2011;10:1056-1064. (Lead author: Dr WO Cooper, Division of General Pediatrics, Vanderbilt University, Nashville, TN).

COMMENT. Confounders in the above study unaccounted for include the unapproved use of stimulants and the uncertainty of diagnosis of ADHD in children younger than 6 years. Although some studies have failed to demonstrate an increased risk of stimulant-associated serious cardiovascular events, one study provides convincing evidence and reason for concern. In a case-control study of mortality data among children and adolescents ages 7 through 19 years, 10 (1.8%) of 564 cases of sudden unexplained death occurred in subjects taking stimulants, whereas only 2 (0.4%) of 564 who died in motor vehicle accidents had taken stimulants. (Gould MS et al. **Am J Psychiatry** 2009;166(9):992-1001).

The need for cardiovascular risk screening before starting stimulant medication in children with ADHD is controversial. The American Heart Association initially advised routine pretreatment ECG (with later modification) whereas the American Academy of Pediatrics considers routine ECG to be unnecessary. Cardiac history and examination are recommended, and ECG and cardiac consultation only if clinically indicated. (Perrin JM et al. **Pediatrics** 2008;12;451-453). Pretreatment ECG and/or cardiac consultation indications are suggested as follows: heart murmur, high blood pressure, palpitations, or syncope, and personal or family history of early heart disease. Involvement in competitive sports might also be added as an indication for pretreatment ECG in adolescents. The cardiologist may clear the child for stimulant medication, but the treating physician makes the final decision to treat or not to treat in each individual case.

EFFECT OF METHYLPHENIDATE ON PUBERTY IN ANIMALS

Researchers at the National Institutes of Health, Bethesda, MD, studying the genetic and behavioral effects of methylphenidate (MPH) in juvenile male rhesus monkeys, observed after 14 mo of treatment a delay in puberty with impaired testicular descent and reduced testicular volume. Testicular volume was significantly reduced ($P<0.05$) at months 15 to 19 and month 27 after high oral doses 12.5 mg/kg twice a day. Significantly lower serum testosterone levels were detected in both the low 2.5 mg/kg dose ($P=0.0017$) and high 12.5 mg/kg dose ($P=0.0011$) animals through month 33 of treatment. Serum inhibin B levels increased in low-dose animals ($P=0.0328$) but differences between groups disappeared by the end of the study. The findings indicate that MPH administration, beginning before puberty, and with clinically relevant blood levels of the drug, impaired pubertal testicular development until -5 years of age. MPH started before puberty either delayed initiation of the onset of puberty or reduced the rate of testicular and pubertal development.

Deficits in testicular volume and testicular secretion resolved over the 40-month observation period, which suggests that the effect of MPH on puberty is not permanent. (Mattison DR, Plant TM, Lin HM, et al. Pubertal delay in male nonhuman primates (Macaca mulatta) treated with methylphenidate. **Proc Natl Acad Sci** USA Sep 27, 2011;108(39):16301-6. Epub 2011 Sep 19)(Lab Reports. ADHD drug may affect puberty. **JAMA** Nov 2, 2011;306(17):1853).