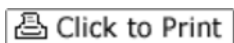




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Pediatric Use of Stimulants Linked to Sudden Death

By Todd Neale, Staff Writer, MedPage Today

Published: June 15, 2009

Reviewed by [Dori F. Zaleznik, MD](#); Associate Clinical Professor of Medicine, Harvard Medical School, Boston and Dorothy Caputo, MA, RN, BC-ADM, CDE, Nurse Planner

LITTLE FALLS, N.J., June 15 -- Use of stimulants is associated with an increased risk of sudden unexplained death among children and teens, a case-control study showed.

Among 564 children and teens who died suddenly, 1.8% were taking stimulants, a figure significantly higher than the 0.4% who were taking the drugs among those in the control group who died in car accidents, reported Madelyn Gould, Ph.D., M.P.H., of the New York State Psychiatric Institute (NYSPI) and Columbia University in New York City, and colleagues.

"Although sudden unexplained death is a rare event," they said, "this finding should be considered in the context of other data about the risk and benefit of stimulants in medical treatment," they noted online in *The American Journal of Psychiatry*.

The study authors acknowledged that the case-control study design prohibited conclusions to be drawn about causality and that there was not enough information to determine whether the children taking stimulants had attention deficit hyperactivity disorder (ADHD).

Nevertheless, "it is clear that the great majority of children and adolescents in the U.S. who are receiving stimulants are receiving them for a clinical diagnosis of ADHD and so, in that sense, these data are relevant for the management of ADHD," said study co-author Mark Olfson, M.D., M.P.H., also of Columbia and the NYSPI.

William Pelham Jr., Ph.D., director of the Center for Children and Families at the State University of New York at Buffalo and not involved with the study, said he thought the findings would establish that, "from a risk-benefit perspective, there is no justification for using stimulants as a first-line treatment [for ADHD]."

"I believe this study will add substantially to recent papers that establish that stimulant drugs, while useful for a minority of ADHD children when needed as a short-term adjunct to psychosocial treatments, have no long-term effects other than serious side effects," including growth suppression, sudden death, and substance use, he said.

But in a conference call, representatives from the FDA, which partially funded the study, said the findings should not affect the way stimulants are prescribed.

"Given the limitations of the study's methodology, we are unable to conclude that these data affect the overall risk and benefit profile of stimulant medications used to treat ADHD in children," said Robert Temple, M.D., of the FDA's Center for Drug Evaluation and Research.

Specifically, he said there was uncertainty about whether all stimulant users were identified. If just one more child in the control group were identified as a user, then the difference between the two groups would become statistically nonsignificant, he said.

Reports of cases of sudden unexplained death among children taking stimulants for ADHD have raised concerns over use of the medications.

The FDA's adverse event reporting system identified 11 sudden deaths in pediatric patients taking methylphenidate (Ritalin and others) from January 1995 to February 2005.

The rate of sudden death is very low, although reported events might underestimate actual rates, the researchers said.

But the issue has yet to be resolved, and in 2006, two FDA advisory committees came to opposite conclusions regarding the need to include a boxed warning of the risk of sudden death on stimulant labels.

Action Points

- Explain to interested patients and parents that the overall risk of sudden unexplained death with stimulant use was low.

Later that year, information was added to the regular warnings section of the medication labels noting the association between sudden death and stimulant use at standard doses in children with structural cardiac abnormalities or other serious heart problems. (See [Cardiovascular Safety Warning Added for Stimulants for ADHD](#))

Last year, the American Heart Association recommended considering routine ECGs before starting children with ADHD on stimulants and other psychotropic therapies and called for future studies to assess the risk of sudden death. (See [AHA Recommends ECG Before Starting Stimulant Therapy for ADHD](#))

Dr. Gould and her colleagues conducted an analysis of a study originally designed to assess the risk of sudden death in children and teens taking tricyclic antidepressants from the mid-1980s to the mid-1990s, which predated the 1996 approval of the combination of amphetamine and dextroamphetamine (Adderall).

They identified 564 cases of sudden death resulting from unknown causes or cardiac dysrhythmia in patients ages 7 through 19 across the U.S. For a control group, they identified 564 children and teens who died as passengers in car crashes.

A comparison group of deceased youths was necessary to reduce recall bias, the researchers said.

The use of amphetamine, dextroamphetamine, methamphetamine, or methylphenidate was determined using interviews with parents, medical examiner records, toxicology findings, and death certificates.

Children and teens who died suddenly for no apparent reason were 7.4 times more likely to be taking stimulants than the controls (OR 7.4, 95% CI 1.4 to 74.9).

In all 10 of the sudden unexplained deaths that involved stimulant use, the researchers identified use of methylphenidate. Of the two stimulant users in the control group, one was taking methylphenidate and one was taking amphetamine.

The researchers were not able to collect information on the dose and duration of stimulant use.

Dr. Gould and her colleagues acknowledged that the study was possibly subject to recall bias, despite the use of a deceased control group.

Additional limitations included inconsistent completion of toxicology assays, which may not have been sensitive enough to detect therapeutic levels of these drugs, and the ability to include only 61% of the cases of sudden unexplained death identified during the study period.

"Ultimately," said David Fassler, M.D., of the University of Vermont in Burlington, "we need more large-scale, long-term studies to help us better understand the overall impact of treatment on morbidity and mortality."

He added that he did not think the findings would alter clinical practice.

In an accompanying editorial, Benedetto Vitiello, M.D., and Kenneth Towbin, M.D., of the National Institute of Mental Health in Bethesda, Md., said the findings of the study "should underscore that stimulants are not innocuous and that their therapeutic use requires careful diagnostic assessment, diligent safety screening, and ongoing monitoring."

"However," they continued, "it is equally clear that sudden unexplained death is a rare event, this is only the first such study, it relies on small numbers, and it is not possible to quantify the risk beyond estimating that it is very small."

They added that because of the rarity of sudden unexplained death, randomized controlled trials would not be practical and that case-control studies "are probably the highest level of evidence that we will be able to obtain about this problem."

The FDA is conducting two ongoing trials -- one in children and one in adults -- evaluating cardiovascular risk in patients taking stimulants. Results are expected to be released either later this year or early next year.

The study was supported in part by a contract from the FDA and a grant from the National Institute of Mental Health.

Dr. Gould reported that she had no conflicts of interest. Her co-authors reported potential conflicts of interest with AstraZeneca, Pfizer, Eli Lilly, Janssen, Johnson & Johnson, Otsuka, and Forest.

The editorialists reported that they had no conflicts of interest.

This article was developed in collaboration with ABC News.



Primary source: The American Journal of Psychiatry

Source reference:

Gould M, et al "Sudden death and use of stimulant medications in youths" *Am J Psychiatry* 2009; DOI:

10.1176/appi.ajp.2009.09040472.

Additional source: The American Journal of Psychiatry

Source reference:

Vitiello B, Towbin K "Stimulant treatment of ADHD and risk of sudden death in children" *Am J Psychiatry* 2009; DOI:

10.1176/appi.ajp.2009.09050619.

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 [Jeanne James, MSW, LCSW](#) - Jun 16, 2009

I am very concerned about this article. We know, as the article suggests, that car accidents are one of the highest causes of death for adolescents. Perhaps if some of the adolescent drivers killed had been diagnosed with ADHD, and were taking medication for their ADHD, they would not have experienced the lack of impulse control and poor judgment which contributed to the accidents that killed them and perhaps others. We also know that children taking medication for ADHD are less likely to become addicted to illegal drugs including alcohol. How many undiagnosed and treated adolescents and later adults die from issues related to their addiction. We also know that the black box warning on medication for treating depression in children and adolescents has resulted in fewer diagnoses and more suicides. Do we really want to "go down this path" with medicinal diagnosis and treatment for ADHD?

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