

## Stimulant Treatment of ADHD and Risk of Sudden Death in Children

Stimulants have been used for the treatment of children with developmentally abnormal levels of motor activity, impulsivity, and inattention for more than 60 years. The validity of attention deficit hyperactivity disorder (ADHD) as a clinical construct is well documented, and the effectiveness of stimulants in improving symptoms has been repeatedly proven in many controlled clinical trials and by meta-analyses (1, 2). Since the 1980s, their use has increased, and it is estimated that about 2.5 million children currently receive these medications in the United States. In addition, use has expanded among adults as well, who account for an increasing proportion of the prescriptions.

Concerns that stimulants may increase the risk for sudden unexplained death in childhood have surfaced repeatedly in case reports and small case series since the early 1990s (3). In 2006, the Food and Drug Administration requested that the package insert of stimulant medications contain a warning that “stimulant products 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” (4). The current prescribing label instructions emphasize that children should receive a physical examination and a review of personal and family history for relevant cardiac events prior to starting stimulant treatment. Current practice guidelines also recommend pretreatment ECG screening when abnormalities are detected through history or physical examination (5, 6), and some experts advocate pretreatment ECG screenings for all children (7).

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The report by Gould and coworkers in this issue is the first methodologically rigorous study to identify a link between therapeutic use of stimulant medication and sudden unexplained death in children without demonstrated heart abnormalities (8). Using a retrospective, case-control design, the investigators matched children who had died of sudden unexplained death to children who had died as passengers in motor vehicle accidents. Medical and treatment information was collected from autopsy reports, toxicology results, and direct interviews with the parents. Cases with identified heart abnormalities or family history of sudden unexplained death were excluded. Of the final sample of 564 cases, 10 (1.8%) of the sudden unexplained death cases were treated with a stimulant at the time of their death, as compared with only two (0.4%) of the motor vehicle accident victims.

What are the implications of these results for further research and clinical practice? An answer requires understanding the limitations of retrospective case-control methods. Although studies employing this design can be highly informative, they are particularly vulnerable to biases (9). A strength of this report is the painstaking lengths the investigators went to in order to reduce possible sources of bias. They used multiple sources of information to confirm stimulant use and conducted a series of sensitivity analyses, the results of which did not change the main conclusion.

However, important confounders may remain. For example, the methods did not allow the investigators to learn whether, independent of stimulant treatment, ADHD itself in-

creased the risk for sudden unexplained death. This is a plausible hypothesis given the association between ADHD and engagement in high-risk behaviors, such as substance abuse. Although history or postmortem toxicological evidence of substance abuse was reason for exclusion from the study, the sensitivity of these screening procedures is not perfect, and other drugs could have been ingested or inhaled. Furthermore, the parents of 40% of eligible cases could not be found or would not provide information. As the investigators point out, there is also a risk of inequality in the effort to search for medical explanations (including medication use) in sudden unexplained death, given its unexplained nature, compared to death from motor vehicle accidents, so that stimulant use might have been missed in the motor vehicle accident comparison population.

The rarity of sudden unexplained death makes randomized prospective studies impractical. Although imperfect, case-control studies are probably the highest level of evidence that we will be able to obtain about this problem. In any event, it would be informative to conduct a replication study, for example examining the sudden unexplained death cases that have occurred since 1996 (the report used data from 1985 to 1996), and to search large clinical population databases for converging evidence. Gould and co-workers cited a study that found no sudden unexplained deaths when analyzing data on over 125,000 person-years from 10-year stimulant use in Florida (11). However, even larger databases are needed to detect rare events such as sudden unexplained deaths.

In the absence of diagnostic biological markers, the accuracy of a diagnosis of ADHD currently rests on careful evaluation and integration of data from multiple informants. However, epidemiological studies suggest that a considerable proportion of stimulant prescriptions are for children who do not meet the criteria for ADHD, although they may suffer from other behavioral or learning disturbances (12, 13). Furthermore, there is evidence of misuse and diversion of stimulants among high school and college students (14). The cognitive effects of stimulants, which improve performance on a variety of tasks even in non-ADHD individuals, have increased their popularity among the public at large and spurred debate about their use as cognitive enhancers (14).

The report by Gould et al. should underscore the fact that stimulants are not innocuous and that their therapeutic use requires careful diagnostic assessment, diligent safety screening, and ongoing monitoring. More research is required to improve the sensitivity of screening methods for heart conditions that increase the risk for sudden unexplained death. Unfortunately, this report cannot assist in resolving the debate over the value of pretreatment ECG screening because ECGs were not systematically obtained for any of these individuals. An ECG can detect heart conduction disorders, such as QT prolongation or Wolff-Parkinson-White syndrome, which increase the risk for sudden unexplained death but are not identifiable postmortem.

These data suggesting a link between sudden unexplained death and a medication commonly used to treat ADHD cannot be dismissed because the sympathomimetic activity of stimulants provides biological plausibility for cardiovascular effects (3). However, it is equally clear that 1) sudden unexplained death is a rare event, 2) this is only the first such study, 3) it relies on small numbers, and 4) it is not possible to quantify the risk beyond estimating that it is very small. A full estimate of the risk-benefit ratio of ADHD treatment cannot be properly conducted at the population level because sudden unexplained death is so rare and we lack controlled long-term data on the effectiveness of these medications for reducing the risk for other adverse health outcomes, such as accidents, medical hospitalizations, unsafe sex practices, antisocial behavior, and substance abuse, which have been associated with ADHD.

ADHD is heterogeneous with respect to symptoms and severity of impairment. A number of treatment options are available, including also nonpharmacological behavioral interventions, which, although less effective than stimulants in the acute control of symptoms, can help children with milder symptoms. When making treatment decisions, clinicians need to apply the current, still incomplete, evidence to the care of indi-

vidual patients by carefully considering the type and severity of symptoms, availability of different treatments, expected benefits, and potential risks.

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**BENEDETTO VITIELLO, M.D.  
KENNETH TOWBIN, M.D.**

*Address correspondence and reprint requests to Dr. Vitiello, Division of Services and Intervention Research and Mood and Anxiety Disorders Program, Division of Intramural Research, NIMH, Rm. 7147, 6001 Executive Blvd., Bethesda, M.D. 20892–9633, [bvitiell@mail.nih.gov](mailto:bvitiell@mail.nih.gov) (e-mail). Editorial accepted for publication May 2009 (doi: 10.1176/appi.ajp.2009.09050619).*

*The authors report no competing interests.*

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