

MEDICATION SAFETY

Stimulant Medications and Sudden Death

By Ann Abramowitz, PhD, and Susanna Visser, MS

A RECENT STUDY ENTITLED “SUDDEN DEATH AND USE OF STIMULANT MEDICATIONS IN YOUTHS”

by Madelyn Gould, PhD, MPH, and colleagues, has raised great concern in the AD/HD community and beyond. In the study the authors sought to test the hypothesis that stimulant exposure increases the risk of sudden death among youth. Two groups of youth were studied, with the frequency of stimulant exposure compared between youth who died of sudden unexplained death and youth who died as passengers in a motor vehicle crash. The primary finding of this study was that there was greater exposure to stimulants among the group of youth who died of sudden unexplained death. This association has been interpreted by some to mean that stimulants may cause sudden death in youth. However, the authors of this study were careful to describe a number of limitations that should be considered when interpreting the study findings. In addition to these limitations, an editorial was published alongside the original article with further considerations for the reader. Based on our own review of the article, there appear to be several additional limitations that we present here as a means of more completely understanding the potential impact of the findings of this study.

In order to appreciate the strengths and limitations of this study, it is important to understand the study’s design. The authors chose a “matched case-control” design, which is a study design that is powerful for studying outcomes that are especially rare, such as sudden death among youth. One sample consisted of children (ages 7-19) who died suddenly and without a known cause. They died between 1985 and 1996. The other sample (also ages 7-19) consisted of children who died as passengers in motor vehicle accidents involving another vehicle during the same years. Five hundred sixty-four matched pairs were created between children in the two groups; they were matched on gender, age within three years, year of death within three years, and data source. To give a hypothetical example, a 14-year-old male who died in 1992 of an unknown cause with data from medical examiner records and informant report might have been matched with an 11-year-old male who died in 1995 in an automobile accident with data from medical examiner records

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and informant report. The study attempted to compare the rate of stimulant use among the children in each group (ten stimulant users in the sudden unexplained death group and two in the motor vehicle group), and the results indicate that taking stimulant medication was several times more frequent in the sudden death group than the motor vehicle death group. The authors concluded that stimulants may be a contributing cause of sudden death, albeit rare.

Gould et al. acknowledged a number of limitations that should be considered when interpreting the statistically significant association between stimulant use and sudden death. First, the authors noted that although they excluded known causes of death and co-existing physical disorders that can be associated with sudden death, underlying heart conditions may not have been detected. As an example, two of the unexplained cases with stimulant use did not have autopsy data to exclude major heart problems. Second, the authors acknowledge that they had no way to know which of the youngsters had AD/HD and the majority of youth taking stimulants likely have AD/HD. Therefore, it was not possible to determine if AD/HD in the absence of stimulants was independently associated with sudden death. Another acknowledged limitation relates to the possibility that stimulant medication, if used, would be more likely to be present in a medical examiner’s report involving unexplained sudden death than it would be in cases involving automobile accidents, where the fact that the child was taking a stimulant likely would not have been considered important at the time. On the other hand, the association between stimulant use and sudden death was actually stronger when cases based just on information from medical examiner or toxicology reports were excluded.

The editorial by NIMH researchers Benedetto Vitiello, MD, and Kenneth Towbin, MD, that accompanied the Gould et al. report addressed some additional limitations of the study, and advised caution in its interpretation. It highlighted the high rate of high-risk behaviors, such as substance abuse, in the AD/HD population that may better explain an increased risk for sudden death in the population.





We agree; in addition, children who take stimulants may have other characteristics that predispose them to sudden death—e.g., other diagnoses, such as neurological disorders.

In addition to the limitations discussed above, several other study limitations should be considered when trying to understand a possible relationship between stimulant medication and sudden death. Chief among our concerns is that the recalled rate of stimulant use in the control group is much lower than what we know was the rate of stimulant use in the general population in that time period. In fact, the rate (0.4%) in the control group is so much lower than the population rate among youth of similar ages for the time period (1.4% by Jensen et al., 1999; 2.7% by Zuvekas et al., 2006) that we wonder about either the quality of the recall or the appropriateness of the control group. The authors state that the rates of stimulant use are consistent with the rates of the time period and cite three sources. However, the rates in those three sources are all higher than those of the comparison group. This lends support to our hypothesis that recall of use of stimulants was understated for the comparison group, probably because of the delay in reporting and the fact that the cause of those youngsters' death was known.

A second limitation that is worthy of mention is the inability of Gould and colleagues (based on recognized limitations in the data sets) to match the subject pairs on race and geographical region, with the result being unequal distributions of these factors across the two study groups. Race and region are related to AD/HD diagnosis and medication rates and vehicular death rates (CDC, 2005; CDC, 2009). Therefore, the apparent association between stimulant exposure and sudden death may have been influenced by these demographic factors. The authors do not discuss the potential influence of these measured factors in their analysis, and, thus, the conclusions appear based on an assumption that the pairs were well matched. Future studies that extend the study years to the present may allow for a larger sample and greater matching success.

We recognize that this would likely require an increase in the range of years allowed when matching on year of death, but it is unlikely that increased variability on this factor would result in as much potential bias as that risked by failing to match on either race or region.

Gould and colleagues recognize that problems with informant recall were an important potential source of bias in their study. They conducted several sensitivity analyses that excluded those youth with the greatest potential for recall bias (e.g., those with the longest recall periods). However, the authors dismiss a potential source of recall bias that we find important. They posit that parents of children who died in vehicular accidents versus unexplained situations would not differentially recall their children's stimulant use. We believe that a parent or other informant may commit to memory all the child's medications when searching for a medical explanation for a child's sudden death, but not necessarily following a vehicular death, for which the cause of death is clear.

What does this mean? First, the study by Gould et al. was initiated after the discovery that 25 adverse events (including sudden death and cardiovascular events) were reported to the FDA between 1999 and 2003, following exposure to a stimulant (Nissen, 2006). Given the estimate that 2.5 million youth and 1.5 million adults were taking medication for AD/HD in 2003, it is likely that if an association exists between stimulant exposure and sudden death, the risk is very small. However, this study adds to the very small body of knowledge on sudden death and stimulant exposure, and we concur with the authors that more research is needed in this area. Any potential risk for such adverse events, no matter how small, warrants research attention. However, given the imprecise nature of the association and the limitations noted by Gould and colleagues, Vitiello and Towbin, as well as those noted above, we concur with the FDA in their recommendation that the findings of this study are insufficient to indicate a change in the care of children with AD/HD. ●

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