Reference

1. Gould MS, Walsh BT, Munfakh JL, Kleinman M, Duan N, Olfson M, Greenhill L, Cooper T: Sudden death and use of stimulant medications in youths. Am J Psychiatry 2009; 166:992–1001

ASHWINI NADKARNI, M.D.
Boston, Mass.
ERIC G. SMITH, M.D., M.P.H.
Worcester, Mass.

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Increased Risk of Sudden Death Among Youths and Stimulant Use: Determining Alternate Potential Factors

To the Editor: Dr. Gould et al. (1) retrospectively determined the stimulant use rate in children/adolescents who died suddenly without explanation and in a matched comparison group who died as passengers in motor vehicle accidents. They identified stimulant use in 1.8% of the group that died suddenly without explanation and in 0.4% of the motor vehicle accident group. They concluded that this difference was the result of an increased risk of sudden death associated with stimulant use. In order to determine the validity of this conclusion, however, additional questions need to be considered.

Although Dr. Gould et al. stated that these rates of stimulant use were comparable to the general population, this was true only for the group that died suddenly without explanation. Olfson et al. (2) reported that the general child/adolescent population rate of stimulant use during the time period assessed in the study ranged from 0.6% in 1986 to 2.4% in 1997. The 1.8% rate in the group that died suddenly without explanation is approximately what would have been found in a random population sample during this 10-year period. If stimulants significantly increase the risk of sudden death, wouldn't we expect the group that died suddenly without explanation to have had a higher than average rate of stimulant use?

Moreover, why was the detected rate of stimulant use in the comparison group (0.4%) so much lower than the population average? Could stimulant use have been underdetected in the motor vehicle accident group? If stimulant use was underdetected in this study, is it possible to know whether the two groups were subject to the same degree of underdetection?

The authors reported collecting stimulant use data from three sources (family surveys, toxicology reports, and medical examiner reports), but they acknowledged that all three sources of data were available for only 10% of the paired comparisons. Most of the comparisons seem to have been based on only a single data source. Is it possible that reliance on a single data source could have contributed to underdetection or even biased detection? The medical examiner reports appear to have been the primary basis for more than one-half of the comparisons. Is it realistic to expect that medical examiners would have been as likely to collect accurate information on psychotropic medication use in the motor vehicle accident victims as they would for children who died without any apparent cause?

Data from family surveys were used in 44% of the comparisons, but the limited detail provided about how surveys were conducted makes it difficult to assess the quality of these data. Were these direct interviews, or were families simply sent questionnaires? Were parents asked specifically about stimulant use? Finally, 10 to 12 years after the incident, is it realistic to expect that a parent whose child died in a motor vehicle accident would recall his or her child's medications as accurately as a parent whose child died suddenly with no explanation?

References

1. Gould MS, Walsh BT, Munfakh JL, Kleinman M, Duan N, Olfson M, Greenhill L, Cooper T: Sudden death and use of stimulant medications in youths. Am J Psychiatry 2009; 166:992–1001
2. Olfson M, Gameroff MJ, Marcus SC, Jensen PS: National trends in the treatment of attention deficit hyperactivity disorder. Am J Psychiatry 2003; 160:1071–1077

MICHAEL R. JOHNSON, M.D.
Gainesville, Fla.

Dr. Johnson has served on the speaker's bureaus of Shire and Novartis; he has also received research support from AstraZeneca, GlaxoSmithKline, Lilly Research Laboratories, Sanofi-Aventis, Shire, Somerset, Supernus, and Takeda.

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Dr. Gould Replies

To the Editor: The thoughtful letters of Drs. Blume, Rostain, Nadkarni, Smith, and Johnson underscore the importance of examining potential confounding factors other than stimulants that may have been responsible for our observed association between sudden unexplained death and stimulant medications.

Drs. Blume and Rostain cite evidence that stimulants may lower the risk of motor vehicle accidents among adolescents, thereby introducing a bias toward lower stimulant use in our comparison group. However, because we selected a comparison group of individuals who died as passengers in a motor vehicle traffic accident involving another motor vehicle, the benefit ascribed to stimulants would not affect our findings. Passenger comparison subjects were specifically selected because they have been found not to be at greater risk for hyperactivity and other deficits in vigilance, attention, and impulse control (1).

Dr. Johnson expresses concern that stimulant use in our case subjects (1.8%) resembles population rates during the study period and that the rate of stimulant use in our comparison subjects (0.4%) was much lower than population rates. He references rates of 0.6% in 1986 and 2.4% in 1997, from a report by Olfson and colleagues (2). This report, however, indicated that 0.7% of youths (age 3–18 years) in 1987 received at least one stimulant prescription for ADHD and 2.9% of youths (age 3–18 years) in 1997 received at least one stimulant prescription for ADHD. Because of the intermittent nature of stimulant therapy in the community (3), these

1-year treatment rates would be expected to be considerably higher than the point prevalence rates that were the focus of our study. The younger age of the sample reported by Olfson et al. (3–18 years old) would also be expected to yield substantially higher rates of stimulant use (4) than our older study group, 90% of whom were between the ages of 12 and 19 years.

Dr. Johnson further suggests that medical examiner reports may have biased detection. We cannot exclude the possibility that, compared with a passenger motor vehicle fatality, an "unexplained" death may have prompted medical personnel to ask more questions about medications at the time of death. However, the primary analysis remained significant (odds ratio=7.3, 95% confidence interval [CI]=1.4–74.8, p=0.015) following exclusion of the one case subject whose methylphenidate exposure was detected solely by medical examiner report.

Dr. Johnson's last concern focuses on the quality of our surveys. A comparable survey was sent to parents of both groups of children. As noted in our article, the survey included items assessing past medical history, medications taken at the time of death, a list of medical problems, and the use of over-the-counter and prescription medications. A history of sudden death among relatives was also assessed. The items assessing medication use were open-ended and did not ask about any one specific class of medication, including stimulants. The reasons for taking the medication(s), and the frequency and duration of use, were also asked. While we cannot rule out the possibility that parents of children in the sudden unexplained death group remembered stimulant medications more vividly than parents of children who died in accidents, we remain confident that the association of sudden death and stimulant medication use is valid because our sensitivity analyses suggest that the strength of the association was not sensitive to the source of stimulant measurement.

Drs. Nadkarni and Smith raise the possibility that group imbalances in age and year of death might have introduced bias toward lower rates of stimulant use in our comparison group. Yet our case (mean age: 15.76 years old) and comparison (mean age: 15.83 years old) subjects had nearly identical mean ages, and the group distributions did not differ in year of death. Drs. Nadkarni and Smith also hypothesize that unmeasured covariates, such as season of death, income, and rural places of residence, may have not been comparable among the case and comparison subjects and that these covariates may affect the likelihood of receiving a stimulant. We do not have information readily available to address these speculations, but we agree with their expectation that such factors might attenuate, but not likely eliminate, the relationship.

We made rigorous efforts to enhance the comparability of case and comparison subjects that could threaten the validity of our study's findings. Significant associations between sudden death and stimulant medication use in youths call attention to potential risks of stimulant medication and hopefully will increase clinical attention and motivate further study. At the same time, we appreciate the benefits of stimulant medication for youths with ADHD and share concerns that physicians will be discouraged from prescribing stimulants or parents will discontinue their child's medication on their own based on our study's findings.

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MADELYN S. GOULD, PH.D., M.P.H.
New York, N.Y.

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Coalitional Affiliation Rather Than Religiosity Might Explain the Heritability of Church Attendance

TO THE EDITOR: We were struck by the high level of genetic loading of church attendance in adulthood (58% of variance) reported by Kenneth S. Kendler, M.D., and John Myers, M.S., in the October 2009 issue of the *Journal* (1). Church attendance was a factor associated with less alcohol and nicotine consumption in the study. A simple, easily defined behavior, church attendance could be interpreted as a proxy of religiosity, which is a much more complex, multidimensional construct (2). In fact, church attendance belongs to the social religiosity dimension, one of the seven religiosity dimensions derived from a factor analysis the authors performed for their questionnaire data in a previous study (2). The other six religiosity dimensions were general religiosity, involved God, forgiveness, God as a judge, unvengefulness, and thankfulness.

Religiosity as a whole has been shown to be heritable (3) and has been hypothesized to be an adaptation or by-product of our evolution (4). Specific neural correlates to religiosity (i.e., God's perceived level of involvement, God's perceived emotion, and doctrinal/experiential religious knowledge) have been demonstrated (5). For such complex phenotypes, it is very difficult to demonstrate that there is no intermediate factor that more clearly explains the role of genes. Indeed, in the study by Kendler and Myers (1), subjects were all Caucasian male twins born in Virginia, 85% of whom were Protestant, mostly fundamentalist or Baptist. It is not clear that one would find similar results in subjects from another sociocultural context, since regular attendance at religious services can vary widely, from 1.7% (Estonia) to 62.3% (Turkey) in a recent European cross-cultural survey (6). It could then be speculated that the heritable trait captured by church attendance could rather be defined as the disposition to perform socially meaningful rituals in order to reinforce coalitional affiliation, as proposed by Boyer (4). Although this hypothesis is also difficult to prove, the selection (throughout generations) of people with high capacity to reinforce group coalition makes sense, at least regarding breeding potential and surviving in social groups.