Sudden Death and Use of Stimulant Medications in Youths

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Objective: The authors sought to determine whether a significant association exists between the use of stimulants and the rare event of sudden unexplained death in children and adolescents.

Method: A matched case-control design was performed. Mortality data from 1985–1996 state vital statistics were used to identify 564 cases of sudden death occurring at ages 7 through 19 years across the United States along with a matched group of 564 young people who died as passengers in motor vehicle traffic accidents. The primary exposure measure was the presence of amphetamine, dextroamphetamine, methamphetamine, or methylphenidate according to informant reports or as noted in medical examiner records, toxicology results, or death certificates.

Results: In 10 (1.8%) of the sudden unexplained deaths it was determined that the youths were taking stimulants, specifically methylphenidate; in contrast, use of stimulants was found in only two subjects in the motor vehicle accident comparison group (0.4%), with only one involving methylphenidate use. A significant association of stimulant use with sudden unexplained death emerged from the primary analysis, which was based on exact conditional logistic regression (odds ratio=7.4, 95% CI=1.4 to 74.9). A comprehensive series of sensitivity analyses yielded qualitatively similar findings.

Conclusions: This case-control study provides support for an association between the use of stimulants and sudden unexplained death among children and adolescents. Although sudden unexplained death is a rare event, this finding should be considered in the context of other data about the risk and benefit of stimulants in medical treatment.

Reports of sudden death among children and adolescents receiving stimulant medications for treatment of attention deficit hyperactivity disorder (ADHD) have raised concerns about the safety of these agents. There have been reports of pediatric stroke after long-term use of methylphenidate within therapeutic ranges (1). Acute myocardial infarction has been reported in one adolescent taking methylphenidate for an unknown period of time (2) and in another adolescent 1 week after restarting a daily 20-mg prescription of mixed amphetamine salts (3). Cardiac arrest occurred in another adolescent who was taking methylphenidate for ADHD and who had previously had a normal baseline echocardiogram (4). The Food and Drug Administration (FDA), using the Adverse Event Reporting System, reported 11 sudden deaths in pediatric patients taking methylphenidate from January 1992 to February 2005 (5). While the FDA's reporting rate of sudden death in stimulant-treated children was the same as the base rate in the general population, spontaneous reports of sudden deaths may underestimate their true incidence, and limited available information on total number of prescriptions precludes reliable estimates of stimulant exposure (5). Less serious cardiovascular effects have also been reported in association with stimulant medications. An average increase in diastolic blood pressure of 4 mm Hg has been found among stimulant-treated youths in placebo-controlled trials (5, 6). A 10-year analysis of Florida Medicaid claims data revealed that stimulant use among youths diagnosed with ADHD was associated with increases of 20% and 21% in risk of emergency department visits and physician office visits for cardiac symptoms, respectively (7). No cardiac sudden deaths occurred during the 42,612 person-years of current stimulant use; however, as the authors noted, the rarity of sudden death and cardiac mortality in this age group would have necessitated a sample size 16 times larger, i.e., approximately 2,000,000 person-years, to detect a significant difference between the stimulant use and nonuse groups.

There continues to be controversy surrounding whether there exists an association between stimulant use for the treatment of ADHD and serious cardiovascular events, including sudden death, with accompanying debate over clinical recommendations for physicians and families (8, 9). The FDA's Pediatric Advisory Committee in March of 2006 voted unanimously against a black box warning, which had been proposed by an earlier FDA advisory committee, but recommended a warning.
targeted to specific high-risk children, such as those with structural heart defects, cardiomyopathy, or heart-rhythm disturbances (10). In 2008, the American Heart Association recommended considering routine ECGs prior to starting children with ADHD on stimulant and other psychotropic therapy regimens (11) but underscored the need for future studies to assess the risk of sudden death associated with stimulant medication use in children and adolescents. The American Academy of Pediatrics (12) has also highlighted the “absence of scientific data to establish an increased risk of sudden death in individuals receiving stimulant medications.”

The present article provides empirical data on the risk of sudden death and stimulant drug use in children and adolescents. In light of the rarity of sudden death in this age group (estimated at 0.8 to 8.5 cases per 100,000 patient-years) (13, 14), a matched case-control design was employed. The analysis seeks to estimate the strength of association between use of stimulant medications and sudden unexplained death.

**Method**

This study was initiated in 1996, with support from the National Institute of Mental Health (NIMH), to examine the association between sudden death in children and adolescents and the use of tricyclic antidepressants or concomitant methylphenidate and clonidine therapy (15, 16). During the course of the study, there was a marked decrease in the use of tricyclic antidepressants in youths (17) and an associated significant increase in the use of selective serotonin reuptake inhibitors (SSRIs), which led to an attenuation of the clinical relevance of our examination of the association of tricyclic antidepressants and sudden death. Thus, these analyses were not pursued further. In light of concerns over the safety of stimulant medications, the FDA in 2006 requested an expansion of the inquiry of stimulants to include amphetamine, dextroamphetamine, and methamphetamine. The current report focuses on stimulant use among children and adolescents.
Sudden Death and Stimulant Medication Use

Definition of Sudden Unexplained Death

A case of sudden unexplained death was defined as any cause of death listed as ICD-9 codes E798 (sudden death, cause unknown), E799.9 (other unknown and unspecified causes), or E427 (cardiac dysrhythmia). These codes reflected causes of death in case reports of sudden death in children using tricyclic medications (15), consistent with the original goal of the study. We targeted cases 7 through 19 years of age, identified from mortality data from 1985–1996 state vital statistics across the United States. We completed our study by using unique; an individual motor vehicle accident victim was matched to one and only one case of sudden unexplained death. Limitations in the pool of comparison subjects precluded matching on unique variables because they have been found not to be at greater risk for hyperactivity and other deficits in vigilance, attention, and impulsivity. Thus, we avoided inappropriately increasing the likelihood of stimulant use among the comparison group. In this way, subjects were likely to be representative of the general population of youths 7 through 19 years of age. The same exclusion criteria noted for sudden unexplained death subjects were applied to the motor vehicle accident victims.

Comparison Group

Individuals who died as passengers in motor vehicle traffic accidents with another motor vehicle (ICD-9 code E812.1) were also examined. A comparison group of deceased youngsters was necessary to avoid differential recall biases. Parents of both sudden unexplained death and motor vehicle accident victims had experienced a sudden, traumatic loss of their children. Unlike other victims of injuries (28), motor vehicle passenger victims were selected because they have been found not to be at greater risk for hyperactivity and other deficits in vigilance, attention, and impulsivity. Thus, we avoided inappropriately increasing the likelihood of stimulant use among the comparison group. In this way, subjects were likely to be representative of the general population of youths 7 through 19 years of age. The same exclusion criteria noted for sudden unexplained death subjects were applied to the motor vehicle accident victims.

TABLE 2. Demographic Characteristics of Sudden Unexplained Death Cases and a Matched Comparison Group of Motor Vehicle Passenger Fatalities

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sudden Unexplained Death Cases</th>
<th>Motor Vehicle Passenger Fatalities</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Excluded From Study (N=362)</td>
<td>Included in Study (N=564)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>14.33</td>
<td>3.81</td>
<td>15.76</td>
</tr>
<tr>
<td>Gender</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Male</td>
<td>221</td>
<td>61.0</td>
<td>347</td>
</tr>
<tr>
<td>Female</td>
<td>141</td>
<td>39.0</td>
<td>217</td>
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<tr>
<td>Race</td>
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</tr>
<tr>
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<td>206</td>
<td>56.9</td>
<td>366</td>
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<tr>
<td>African American</td>
<td>114</td>
<td>31.5</td>
<td>139</td>
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<tr>
<td>Hispanic</td>
<td>30</td>
<td>8.3</td>
<td>38</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
<td>0.8</td>
<td>4</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>6</td>
<td>1.7</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>0.8</td>
<td>8</td>
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<tr>
<td>Region of death</td>
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<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>73</td>
<td>20.2</td>
<td>103</td>
</tr>
<tr>
<td>South</td>
<td>194</td>
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<tr>
<td>West</td>
<td>34</td>
<td>9.4</td>
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<td>Midwest</td>
<td>61</td>
<td>16.9</td>
<td>118</td>
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<tr>
<td>Year of death</td>
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</tr>
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<td>1985</td>
<td>42</td>
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<tr>
<td>1996</td>
<td>17</td>
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<td>51</td>
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</table>

Exclusions were applied to exclude deaths caused by accidental deaths, suicides, overdoses, homicides, and other unnatural causes (e.g., asthma) initially misclassified on death certificate (as accidental death, suicide, homicide, and other causes). Cases were matched on unique variables because they have been found not to be at greater risk for hyperactivity and other deficits in vigilance, attention, and impulsivity. Thus, we avoided inappropriately increasing the likelihood of stimulant use among the comparison group. In this way, subjects were likely to be representative of the general population of youths 7 through 19 years of age. The same exclusion criteria noted for sudden unexplained death subjects were applied to the motor vehicle accident victims.

Methodology

The primary exposure variable was evidence of stimulant use immediately prior to death, indicated by presence of amphetamine, dextroamphetamine, methamphetamine, methylpheni-
date, or their derivatives, as noted by informants or in medical examiner records, toxicology findings, or death certificates. Information was also obtained about use of clonidine, tricyclic antidepressants, and SSRI antidepressants.

Sources of Data

Mortality data and death certificates were obtained from state vital statistics offices across the United States (including New York City and the District of Columbia) for 1985 through 1996. Indiana, Kansas, Maryland, Wisconsin, and Wyoming were excluded because their state statutes did not allow direct interviewing of families of deceased individuals or had restrictive contact requirements.

For informant reports, the names of the deceased child and his or her parents and the address at time of death were identified from the death certificate, on public record, from the state vital statistics offices. Parents were approached by letter describing the purpose of the study and were asked to complete a survey. The survey included items assessing medical history, medications taken at 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. To locate informants, various Internet search engine white pages, a credit bureau database (without access to credit information), ChoicePoint (CDB Infotek), and PrivateEye were used.

Medical examiner records and toxicology findings were used to identify medication use and assist in the identification of exclusion criteria. Medical examiner reports could include informant- or toxicology-based findings, as well as autopsy reports. The applied postmortem detection threshold for a blood or urine stimulant level to be deemed positive varied considerably across jurisdictions. Thus, our reports of a positive finding reflect a value above the stated threshold for each individual laboratory.

Procedures

Data collection, from March 1997 to January 2008, involved the following phases. Cases of sudden unexplained death were identified through state mortality data, and death certificates were obtained from state vital statistics offices. Death certificates were reviewed for eligibility by the research team. Parents were approached for surveys and consent for records, if required by state law. Autopsy and toxicology records obtained from medical examiners were reviewed and abstracted. The same procedures were applied to motor vehicle accident victims matched to sudden unexplained death cases with surveys or toxicology results.

A two-stage determination of eligibility for all subjects was conducted by the two principal investigators (M.S.G. and B.T.W.) and research staff, blind to medication status. The first stage involved the examination of death certificates, and the second involved review of informant reports and medical examiner, autopsy, toxicology, and medical records.

The Institutional Review Board of the New York State Psychiatric Institute/Columbia University Department of Psychiatry approved study procedures, and a Certificate of Confidentiality was issued by NIMH.

Analytic Strategy

The basic unit of analysis is the matched dyad, rather than the individual subject. We estimated the association between sudden unexplained death and stimulant exposure using a logistic regression model that predicted sudden unexplained death from stimulant exposure. Race and region of death were included as covariates in all logistic regression models. In light of matching on sources of information (e.g., medical examiner records, toxicology, and informant reports), only sources available for both members of the matched pair were used to define exposure status. In the primary analysis, using the total sample, exposure was defined as any stimulant indication. A series of sensitivity analyses varied the exposure definition, including the presence of any stimulant as noted by informants; any stimulant reported in medical examiner records or toxicology reports; methylphenidate reported by any source; methylphenidate noted by informants; and methylphenidate disclosed in medical examiner records or toxicology reports. Each sensitivity analysis used the subsample of dyads with observed data for the specific information source.

In light of the original study’s intent to examine the association of sudden death with tricyclic antidepressants and with concomitant methylphenidate and clonidine use, we conducted another series of analyses to assess whether these associations might be significant in our sample in order to determine whether the concomitant use of these medications needed to be taken into account in our current sensitivity analyses of stimulant exposure.

Pairing of subjects (27) was incorporated into the conditional logistic regression model through exact conditional logistic regression using the EXACT statement in the LOGISTIC procedure in SAS statistical software, release 8.1.

Results

Eligible individuals (N=926) were identified from a pool of 3,211 youths with deaths listed as ICD-9 codes E798, E799.9, or E427 (Figure 1). Table 1 provides the reasons for ineligibility. The overall study inclusion rate was 60.9% (N=564 of 926). Study exclusion was due largely to our inability to locate informants listed on the death certificates and obtain medical examiner or toxicology records. There were no significant differences in gender or race between the sudden unexplained death cases included and excluded from the study. However, there were significant differences in age, region of death, and year of death (Table 2).

The group of 564 comparison subjects was obtained from a potential pool of 1,014 motor vehicle passenger fatalities, identified from jurisdictions that conducted informative toxicology screens. Thus, 55.6% of the total pool of motor vehicle passenger fatalities were matched to a sudden unexplained death case. Table 2 displays the demographic characteristics of the sudden unexplained death cases included in the study and the motor vehicle accident comparison group; race and region of death significantly differed between the two groups. The distribution of the information sources available for the 564 matched pairs was as follows: informant reports only (29.6%); medical examiner records or toxicology reports only (55.5%); informant reports and medical examiner records but no toxicology report (5.3%); and all three sources (9.6%).

Matched Pair Analyses

Ten of the 564 sudden unexplained death cases (1.8%) were identified as having used stimulants at the time of their deaths (Table 3). In each of these cases, the stimulant detected was methylphenidate. Stimulants were identified in two of the 564 motor vehicle accident comparison subjects (0.4%). Detailed information on the dose or duration of stimulant use was not available. Rates of stimulant use among subjects fell within the range reported for the years of study (26, 28, 29). Results of the primary analysis and sensitivity analyses are presented in Table 4, and the rates...
of exposure in the groups for each of these analyses are presented in Figure 2. The odds ratio derived from the primary exact logistic regression was 7.4 (95% CI=1.4–74.9; \(p=0.02\)). Sensitivity analyses using alternative measures of stimulant exposure revealed qualitatively similar findings, indicating that qualitatively our finding is insensitive to the stimulant exposure algorithm. In particular, all odds ratios observed were clinically significant (31), with the smallest one being 4.2 for the scenario “any stimulant, limited to medical examiner/toxicology reports.”

Preliminary analysis of the association of tricyclic antidepressants with sudden death indicated that they might be associated in our sample (six exposures among our sudden death cases and none among our motor vehicle accident comparison subjects). Thus, another series of sensitivity analyses, paralleling those described previously, was conducted deleting any individuals with concomitant tricyclic antidepressant and stimulant use (Table 4 and bottom half of Figure 2). The sensitivity analyses, excluding the stimulant-exposed sudden death case with concomitant tricyclic antidepressants, yielded essentially the same results, with the smallest odds ratio being 3.2, again for the scenario “any stimulant, limited to medical examiner/toxicology reports.” The use of clonidine appeared not to be associated with sudden death, providing no justification to delete the case with concomitant clonidine and stimulants. In analyses with reduced numbers of total observations or exposures, some of the \(p\) values fell below statistical significance. However, the focus of sensitivity analysis is on the effect sizes (the odds ratios), which reflect the strength of the association, rather than the \(p\) values, which are a function of sample size (31).

### Examination of Potential Biases

Threshold postmortem blood levels of detection of the targeted stimulant exposure varied by jurisdiction, raising the possibility that the thresholds for sudden unexplained death cases might be more sensitive than for the comparison group of motor vehicle accident victims. Mean threshold detection levels available for 83 cases of sudden unexplained death and 66 motor vehicle accident deaths indicated that their thresholds for methylphenidate were not significantly different (mean=127.7 ng/ml versus 108.8 ng/ml, respectively; \(t=1.2, df=147, p=0.23\)).

Since a matched comparison subject was only sought after the identification of a case with appropriate documents, the interval between date of death and informant survey was significantly longer for the comparison subjects (mean=12.8 years, SD=4.5) than the sudden unexplained death cases (mean=9.8 years, SD=5.2) \((t=9.5, df=252, p<0.01)\), suggesting a possible recall bias. However, deleting all three motor vehicle accident victims whose death-to-survey interval was greater than two standard deviations above the mean of the sudden unexplained death cases did not change the results of the matched-pair analysis (odds ratio=7.3, 95% CI=1.4–74.0; \(p=0.02\)). Moreover, the death-to-survey interval was not significantly related to reports of stimulant exposure among sudden unexplained death cases (odds ratio=0.99, 95% CI=0.98–1.01; \(p=0.46\)). An informant survey was available for only one stimulant-exposed motor vehicle accident victim, pre-
cluding the inclusion of motor vehicle accident victims in a similar analysis. The distribution of informants did not significantly differ by group ($\chi^2$=8.1, df=6, p=0.23). A great majority of informants for sudden unexplained death cases (91.2%) and motor vehicle accident victims (93.2%) were parents/legal guardians, suggesting that differential recall bias is unlikely to be an important source of bias.

**Discussion**

In recent years, concerns have arisen that stimulants may be associated with an increased risk of death. Results of the current study are consistent with these concerns. The odds of using stimulant medications were approximately six to seven times greater for the cases of sudden unexplained death than for the matched motor vehicle accident victims. Such an association is biologically plausible given the central and peripheral catecholaminergic effects of stimulants and significant increases in heart rate and blood pressure that accompany their use (32).

The present study has several strengths. First, it employed a matched case-control design, which yielded substantial power to detect rare outcomes. Second, multiple sources of information were used to increase the sensitivity of detecting stimulant use. Third, the availability of parent reports lessened the possibility that the findings reflect illicit stimulant use, since it is unlikely that parents would have known of or reported illicit stimulant use. The single youth who appeared likely to have used stimulants illicitly was a motor vehicle accident victim, whose “positive” exposure was detected by toxicology alone. Fourth, several potential confounding factors, such as asthma, that are associated with both ADHD (33) and sudden death (24), were excluded. Furthermore, because ADHD (34) and impaired attention (35) are common among youths with some congenital structural cardiac diseases, we excluded individuals with evidence of cardiomegaly, cardiac hypertrophy, and cardiomyopathy. Three individuals receiving stimulants were excluded from our group of sudden unexplained death cases because of notations of cardiac hypertrophy, even though the cardiac abnormalities were not cited as the cause of death. Moreover, we deleted a sudden death case with concomitant use of stimulants and tricyclic antidepressants, another possible confounding factor, in a second series of sensitivity analyses, and this had little effect on the results. Fifth, the study’s dates of inquiry (1985–1996) predated the use of Adderall, first approved by the FDA in 1996, which has been the stimulant medication most strongly implicated in sudden death (36).

The study also has important limitations. First, while case-control studies are a powerful method of detecting association, they cannot establish causality. It is conceivable that, despite our rigorous efforts to exclude or adjust for potential confounding factors, some unmeasured factors other than stimulant use were responsible for the observed association. For example, although gross structural cardiac disease was presumably excluded by autopsy, autopsy data were not available for two sudden unexplained death cases with stimulant exposure, and forensic pathology varies substantially in its ability to identify physiological as opposed to anatomic cardiovascular disease. Physiological abnor-
Sensitivity analyses, no concomitant

Sensitivity analyses

998

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as asthma (24, 33), there may be other unidentified mecha-

known presence of structural cardiac diseases (24), as well

with sudden unexplained death. Although we excluded

can we determine whether untreated ADHD was associated

to estimate accurately the rates of ADHD in our sample, nor

was not available for all subjects. Therefore, we are unable

casionally noted in a medical record or by an informant, it

ing their clinical diagnoses. While this information was oc-

mation on the psychiatric status of the decedents, includ-

still yield a significant association.

40% of sudden unexplained death cases were excluded due

tected. However, a sensitivity analysis revealed that even if

significant cardiac abnormalities may have passed unde-

history of long QT or sudden cardiac death, but clinically

malities that confer risk (e.g., cardiac depolarization and re-

polarization abnormalities such as Brugada syndrome and

long QT syndrome) could not be reliably excluded from the

analysis. We attempted to exclude subjects with known pro-

longed QT interval, other conduction disorders, or a family

history of long QT or sudden cardiac death, but clinically

significant cardiac abnormalities may have passed unde-

tected. However, a sensitivity analysis revealed that even if

40% of sudden unexplained death cases were excluded due

to undetected cardiac disease, the primary analysis would

still yield a significant association.

Second, we were unable to systematically obtain informa-

on the psychiatric status of the decedents, including

ting their clinical diagnoses. While this information was oc-

asionally noted in a medical record or by an informant, it

was not available for all subjects. Therefore, we are unable

to estimate accurately the rates of ADHD in our sample, nor

can we determine whether untreated ADHD was associated

with sudden unexplained death. Although we excluded the

known presence of structural cardiac diseases (24), as well

as asthma (24, 33), there may be other unidentified mecha-

nisms that were not controlled.

Third, we attempted to avoid differential recall biases, an

important potential limitation of retrospective case-control

studies, by employing a comparison group of deceased

youths whose parents/legal guardians had also experi-

enced a sudden, traumatic loss of their children. However,

we cannot exclude the possibility that relative to a motor

vehicle passenger fatality, an “unexplained” death may

have prompted medical personnel to ask more questions

about medications at the time of death. Yet the primary

analysis remains significant (odds ratio=7.3, 95% CI=1.4–74.8, p=0.015) following exclusion of the one sudden unex-

plained death case whose methylphenidate exposure was
detected solely from the medical examiner’s report. Al-

though conceivable, we consider it unlikely that parents of

sudden unexplained death cases remembered stimulant

medications more vividly than parents of children who died

in accidents. It is reassuring that medical records available

for two sudden unexplained death cases whose “positive”
exposures were based solely on the parental survey corrob-

orated these informant reports. Because we were unable to

obtain medical records on a majority of our subjects, we did

not use them to identify “positive” exposures.


TABLE 4. Results of Primary and Sensitivity Analyses of Stimulant Exposure in Sudden Unexplained Death Cases and a Matched Comparison Group of Motor Vehicle Passenger Fatalities

<table>
<thead>
<tr>
<th>Analysis and Condition</th>
<th>Number of Matched Pairs in Analysis</th>
<th>Both Positive</th>
<th>Only in Sudden Unexplained Death Case</th>
<th>Only in Motor Vehicle Accident Victim</th>
<th>Both Negative</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
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<td></td>
<td></td>
<td>7.4</td>
<td>1.4–74.9</td>
<td>0.02</td>
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<td>Any stimulant, noted by any source</td>
<td>564</td>
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<td>10</td>
<td>2</td>
<td>552</td>
<td>9.6</td>
<td>0.96–493.1</td>
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<td>Sensitivity analyses</td>
<td>Any stimulant, noted by any source</td>
<td>563</td>
<td>0</td>
<td>9</td>
<td>2</td>
<td>552</td>
<td>6.4</td>
<td>1.1–67.0</td>
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<td>0</td>
<td>6</td>
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<td>Sensitivity analyses, no concomitant tricyclic antidepressants</td>
<td>Any stimulant, noted by any source</td>
<td>563</td>
<td>0</td>
<td>9</td>
<td>2</td>
<td>552</td>
<td>6.4</td>
<td>1.1–67.0</td>
</tr>
<tr>
<td>Any stimulant, limited to informant reports</td>
<td>251</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>244</td>
<td>9.6</td>
<td>0.96–493.1</td>
<td>0.055</td>
</tr>
<tr>
<td>Any stimulant, limited to medical examiner/toxicology reports</td>
<td>396</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>389</td>
<td>3.2</td>
<td>0.4–46.9</td>
<td>0.41</td>
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<tr>
<td>Methylphenidate, noted by any source</td>
<td>563</td>
<td>0</td>
<td>9</td>
<td>1</td>
<td>553</td>
<td>11.6</td>
<td>1.4–544.7</td>
<td>0.02</td>
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<tr>
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<td>0</td>
<td>6</td>
<td>1</td>
<td>244</td>
<td>9.6</td>
<td>0.96–493.1</td>
<td>0.055</td>
</tr>
<tr>
<td>Methylphenidate, limited to medical examiner/toxicology reports</td>
<td>396</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>390</td>
<td>4.2</td>
<td>0.4–208.8</td>
<td>0.36</td>
</tr>
</tbody>
</table>

a Only pairs with the specific source of exposure information were included in specific sensitivity analyses.

b Identical results are shown for the rows “Any stimulant, limited to informant reports” and “Methylphenidate, limited to informant reports” because the only exposures other than methylphenidate were detected in toxicology reports rather than by informants. The one case with concomitant tricyclic medication was not included in the analysis because only a toxicology report was available.

c While Table 3 lists eight sudden unexplained death cases in which stimulant exposure was determined by an informant survey, only six of the eight are included in the sensitivity analyses limited to informant reports because two were not matched to a motor vehicle accident comparison subject with survey data and were therefore excluded from the analyses.
Fourth, toxicological assays were not conducted consistently across jurisdictions and may not have been sufficiently sensitive to detect therapeutic levels of methylphenidate, yielding an unreliable measure of exposure. The average detection threshold in toxicological assays (approximately 100 ng/ml) appeared to be higher than blood levels achieved during routine therapeutic use of immediate-release methylphenidate preparations (24 ng/ml) (37), or the even lower peak plasma levels of 8–10 ng/ml achieved by the more recently marketed single daily dose, long-duration methylphenidate preparations, such as OROS methylphenidate (38). The short half-life of meth-

a TCAs=tricyclic antidepressant medications.
SUDDEN DEATH AND STIMULANT MEDICATION USE

...benidipate (37, 39) and the interval between the last ingestion of medication and the acquisition of the blood samples is another potential source of insensitivity of the toxicology screens. Because sustained-release stimulants had not yet been widely marketed during the years of study (1985–1996), a therapeutic dose may not have remained in the blood for sufficient time to be detected by postmortem toxicology screens. This may explain why stimulants were not detected in the toxicology reports of five sudden unexplained death cases whose stimulant use was reported by the informant or noted in the medical examiner’s record (as reported by an informant at the time of death). Thus, while we are confident that the toxicology screens accurately ruled out overdoses, they may have been insensitive in some cases to therapeutic levels of methylphenidate. Nevertheless, since only sources of information available for both sudden unexplained death cases and matched motor vehicle fatality victims were used in the analyses, limitations in a particular source of exposure, whether toxicology records or informant reports, were comparable across groups. Moreover, sensitivity analyses suggest that qualitatively our results were not sensitive to method of stimulant measurement.

Fifth, we were able to include in our analyses only 61% of the eligible cases of sudden unexplained death. Although there were no significant differences in gender or race between included and excluded subjects, these groups did significantly differ in age, region, and year of death. Sudden unexplained death cases included in the study were significantly older, less likely to have died in the South, more likely to have died in the West, and more likely to have died in the later years of the study. Nationally representative studies indicate that stimulant use rates vary by age, region, and year (26, 28). Differences in age would likely have yielded lower rates of stimulant use among those included because age is inversely related to stimulant use (26, 28). Similarly, since the South has the highest rate of stimulant use and the West has the second lowest rate (26), rates of stimulant use among sudden unexplained death cases included in the study would likely have been lower than in those excluded. Conversely, the steep increase in the utilization of stimulants over time (26, 28, 29) would bias toward more stimulant use among the included than the excluded subjects. Although included subjects are not representative of all sudden unexplained death cases, pairs were either matched (age, gender, and date of death) or adjusted (race and region of death) for these sociodemographic and vital characteristics. Nevertheless, there may be unknown selection biases related to our inability to obtain information from all potential cases.

Last, because the project was originally funded to examine the association of sudden death and the use of tricyclic antidepressant medication, we did not include pediatric stroke and acute myocardial infarction, other causes of death linked to methylphenidate in case reports (1–3, 40).

This may have yielded an underestimation of the association between sudden death and stimulant use.

This study reports a significant association or “signal” between sudden unexplained death and the use of stimulant medication, specifically methylphenidate. While the data have limitations that preclude a definitive conclusion, our findings draw attention to the potential risks of stimulant medications for children and adolescents, which warrant clinical attention and further study.

References


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