COMMENTARY

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Attention-Deficit Hyperactivity Disorder (ADHD) Treatment and Sudden Death

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There has been much recent concern, and consequently much publicity, about the possible cardiovascular effects of medication used to treat attention-deficit hyperactivity disorder (ADHD), in particular the question of whether such medication might be associated with sudden death.[1-6] Against this background, it is interesting to see the publication of population-based studies of mortality associated with ADHD drug treatment, such as that of McCarthy et al.[7] in this issue of *Drug Safety*.

The situation with regard to stimulant medication (methylphenidate, dexamfetamine and related compounds) and sudden death has been summarized well by Wilens et al.,[4] and an up-to-date commentary has been provided by the US FDA.[6] Wilens et al.[4] have made the point that there are over 300 controlled trials of stimulant medication involving more than 5000 subjects, apparently with no sudden death. However, children with pre-existing cardiovascular problems are generally excluded from such trials, raising the question of whether there are specific cardiovascular risk factors for sudden death. Wilens et al.[4] have pointed out that the anatomical characteristics in autopsies in subjects who have had sudden death during stimulant treatment are similar to those reported in sudden death in the general population, although it should be noted that specialist autopsies would be required to detect some cardiac abnormalities.[1] Nevertheless, they state that it would be prudent to follow the guidelines of the American Heart Association panel on psychotropic agents in children and adolescents; specific questions should be asked with regard to family history of premature sudden death (under 30 years of age) and a personal history of syncope, palpitations, chest pain or dizziness of unknown origin. These patients should be examined and investigated more carefully. However, the consensus is that a routine ECG is not necessary for otherwise healthy children.

We have recently reviewed the literature on the cardiovascular effects of stimulant medication and atomoxetine in children with ADHD (Stiefel and Besag: manuscript being prepared for submission). Although there are major limitations with the methodology in many of the studies, it appears to be that grouped mean data reveal small increases in both blood pressure and heart rate that are statistically significant but which are said not to be clinically significant. However, the mean data mask the fact that some individuals had increases in blood pressure and/or heart rate that were sufficiently great to make the clinician decide to stop the medication. This raises the interesting questions of whether more extreme changes in heart rate or blood pressure might occur very rarely and whether such changes might increase the risk of sudden death. The review also revealed that there are almost no data on children with pre-existing cardiac problems, although many of these children have ADHD and, on this basis, would be candidates for treatment with stimulant medication or atomoxetine. Furthermore, there is a lack of data on the long-term effects of small increases in blood pressure or heart rate, and it is consequently not known whether such effects might also increase the risk of sudden death. Our review also revealed

a lack of any consistent data concerning ECG changes with these medications.

It is, perhaps, somewhat reassuring that stimulant medication has been prescribed for many decades and that several million patient-years' experience has not yet revealed any unequivocal cause for concern with regard to the cardiovascular safety of this medication. However, this should not be taken as an excuse for complacency with regard to such an important adverse effect as sudden death.

A particularly interesting contribution to the debate has been provided by the review of Gould et al.,[5] who carried out a matched case-control study on 564 cases of sudden unexplained death in children and young people (aged 7–19 years) and a comparison group who died as passengers in motor vehicle traffic accidents. Ten of the subjects (1.8%) in the sudden unexplained death group were taking stimulants; in fact, the only stimulant taken in this subgroup was methylphenidate. Only two (0.4%) of the comparison group of young people who died in road traffic accidents were taking stimulants, one of whom took methylphenidate. This provided an odds ratio of 7.4 (95% CI 1.4, 74.9), indicating a significant association of stimulant use with sudden death. It should be noted that there were many exclusions, including all deaths of known causes, medical intervention complications or hospitalization for more than 48 hours at the time of a death, co-existing physical disorders known or suspected to be associated with sudden death, Wolff-Parkinson-White syndrome, cerebral palsy, profound developmental delays, seizure disorders, sickle cell anaemia, morbid obesity, asthma, anorexia nervosa, prolonged QT interval in the subject or in a first-degree relative, history of sudden death amongst first-degree relatives, conduction disorders in the deceased, or evidence of cardiac disease or abnormal anatomical findings on autopsy, such as cardiomegaly, cardiac hypertrophy or cardiomyopathy. It is also interesting to note that the investigators did not include acute myocardial infarction, for which there are case reports of death with stimulant medication.[8,9] They carried out a very careful analysis to try to exclude confounding factors. However, the authors have acknowledged that their study had important limitations. The deaths occurred from 1985 to 1996 but the data were collected over a long period from March 1997 to January 2008. This might have affected the reliability of some of the results, particularly those depending on recall of information. Although there were many exclusion criteria, it is theoretically possible that ADHD might be associated with some co-morbidity that was not excluded but could have led to an increased risk of sudden death, independent of the prescription of stimulant medication. The authors could not, for example, exclude undiagnosed conditions that might have predisposed to cardiac arrhythmias.[5] They specifically stated that they were systematically unable to obtain information on psychiatric co-morbidity, and there is an increasing recognition of the fact that psychiatric co-morbidity can be associated with a predisposition to physical disorders; for example, there is good evidence to indicate that depression predisposes to epilepsy.[10] The psychiatric co-morbidity in children with ADHD is high.[11]

The major limitation of any case-controlled study, as acknowledged by Gould et al.,[5] is that it cannot determine causation directly. It can only provide evidence that might *support* a causal link. In theory, the most scientifically sound approach would be to carry out a prospective, randomized, placebo-controlled study of stimulant medication in children with ADHD, but this would be impractical because of the large numbers that would be required to study such a rare adverse event as sudden death. Referring to this study, the FDA recently commented that it was "unable to conclude that these data affect the overall risk and benefit profile of stimulant medication used to treat ADHD in children".[6] In the same document, the FDA made the following recommendations for healthcare professionals:

- take a medical history of cardiovascular disease in a child and his or her family;
- perform a physical examination, with special focus on the cardiovascular system (including examination for the signs of Marfan syndrome);
- consider obtaining further tests such as a screening ECG and echocardiogram if the history or examination suggests underlying risk factors for, or the presence of, heart disease.

The FDA document also recommended that ''Any child who develops cardiovascular symptoms (such as chest pain, shortness of breath or fainting) during stimulant medication treatment should immediately be seen by a doctor''.

What is the contribution of the study by McCarthy et al.[7] to this ongoing debate? The aim of their study was to identify cases of death in patients prescribed stimulant medication and atomoxetine, and to determine any association between these drugs and sudden death. They used the General Practice Research Database (GPRD) in the UK. This computerized database contains anonymized patient data maintained by the Medicines and Healthcare products Regulatory Agency (MHRA) and currently contains data for approximately 3 million active patients, about 5% of the UK population, with a demographic distribution similar to that of the general population. The use of such databases is much better than relying on spontaneous reporting systems, which are said to reveal only a small proportion of cases and could lead to a gross underestimate of the frequency of an adverse effect.[1] McCarthy et al.[7] used the GPRD to identify patients, aged 2–21 years, from 1 January 1993 to 30 June 2006, who had been prescribed methylphenidate, dexamfetamine or atomoxetine. This provided a cohort of 18 637 patient-years. Seven patients from this cohort died, six of whom were not judged to have been cases of sudden unexplained death. There was uncertainty about the remaining case. This allowed the authors to confirm that sudden death is a rare event in children taking stimulant medication for ADHD. If the single case was considered to be a sudden death resulting from the stimulant medication, this would have provided an incident rate ratio of 1.63 (95% CI 0.04, 9.71).

Although it was not the aim of the study, the authors found an interesting and disturbing association between an increased standardized mortality ratio (SMR) for suicide and the prescription of these drugs. Because the definition of suicide used for children is different from that used for adults, the SMRs were presented for the two different age groups: 11–14 years and 15–21 years. The SMRs for suicide were 161.91 (95% CI 19.61, 584.88) and 1.84 (95% CI 0.05, 10.25), respectively, for the two age groups. However, there was no indication that the medication itself was responsible for the apparent increase in SMR; co-morbidity is a much more likely explanation. Why might this finding be relevant? Although there are no data on untreated subjects in this study, if the suicide rate in subjects who were untreated was found to be much higher than in the treated patients, this might imply that the risks of not treating could far outweigh any risks of sudden unexplained death from treatment. At this point, such a hypothesis is pure conjecture but it does emphasize the importance of collecting data on mortality risks from all causes, and then assessing the relative risks and benefits of treatment very carefully. In this context it should be noted that substance misuse might be higher in untreated ADHD subjects,[12] although this issue has also been debated.[13] With regard to sudden unexplained death or, indeed, sudden cardiac death, the study of McCarthy et al.[7] emphasises the point that much larger numbers are needed to answer the question of whether stimulant medication might be responsible. The Agency for Healthcare Research and Quality and the FDA are supporting a large epidemiological study that should provide further information on the risks associated with stimulant medication.[6] Whether this large study will answer the remaining questions remains to be seen.

What should we conclude with regard to the risk of sudden death with medication used to treat ADHD? At this stage, we can only conclude that sudden death is a rare event in children with ADHD but that we do not yet have the data to decide whether there is any causal link with medication prescribed to treat this condition or not. The recommendations of the FDA, as stated earlier, appear to be reasonable: take a personal and family cardiac history; examine the patient; and order investigations only if clinically indicated on this basis. We might add, if in doubt, for patients with known cardiovascular/ECG abnormalities, consult with a specialist cardiologist who is able to give a reliable opinion. What remains clear is that ADHD can often be treated very successfully, improving the lives of both the children and their families. For most children with ADHD, the potential benefits

of treatment would seem far to outweigh the potential risks.

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References

1. Nissen SE. ADHD drugs and cardiovascular risk. N Engl J Med 2006; 354 (14): 1445-8
2. Anders T, Sharfstein S. ADHD drugs and cardiovascular risk [comment]. N Engl J Med 2006; 354 (21): 2296-8
3. Rappley MD, Moore JW, Dokken D. ADHD drugs and cardiovascular risk [comment]. N Engl J Med 2006; 354 (21): 2296-8
4. Wilens TE, Prince JB, Spencer TJ, et al. Stimulants and sudden death: what is a physician to do? Pediatrics 2006; 118 (3): 1215-9
5. Gould MS, Walsh T, Munfakh JL, et al. Sudden death and use of stimulant medications in youths [online]. Available from URL: http://ajp.psychiatryonline.org/cgi/reprint/ajp; 166/9/992 [Accessed 2009 Aug 28]
6. US FDA. Communication about an ongoing safety review of stimulant medications used in children with attention-deficit/hyperactivity disorder (ADHD) [online]. Available from URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165858.htm [Accessed 2009 Aug 28]
7. McCarthy S, Cranswick N, Potts L, et al. Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: a retrospective cohort study of children, adolescents and young adults using the General Practice Research Database. Drug Saf 2009; 32 (11): 1089-96
8. George AK, Kunwar AR, Awasthi A. Acute myocardial infarction in a young male on methylphenidate, bupropion, and erythromycin. J Child Adolesc Psychopharmacol 2005; 15 (4): 693-5
9. Gandhi PJ, Ezeala GU, Luyen TT, et al. Myocardial infarction in an adolescent taking Adderall. Am J Health Syst Pharm 2005; 62 (14): 1494-7
10. Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. Biol Psychiatry 2003; 54 (3): 388-98
11. Dopheide JA, Pliszka SR. Attention-deficit-hyperactivity disorder: an update. Pharmacotherapy 2009; 29 (6): 656-79
12. Wilens TE, Faraone SV, Biederman J, et al. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 2003; 111 (1): 179-85
13. Volkow ND, Swanson JM. Does childhood treatment of ADHD with stimulant medication affect substance abuse in adulthood? [comment]. Am J Psychiatry 2008; 165 (5): 553-5

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