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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

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Abstract

Background: Following reports of sudden death in patients taking medication to treat attention-deficit hyperactivity disorder (ADHD), this study aimed to identify cases of death in patients prescribed stimulants and atomoxetine and to determine any association between these and sudden death.

Method: The UK General Practice Research Database (GPRD) was used to identify patients aged 2–21 years from 1 January 1993 to 30 June 2006 with a prescription for methylphenidate, dexamfetamine or atomoxetine. Patients were followed from the date of first prescription until whichever came first: date of death, transferred-out date, age >21 years or end of the study period.

Results: From a cohort of 18 637 patient-years, seven patients died. Cause of death was obtained for six of the patients. None were deemed to be cases of sudden death. Compared with a general population rate of sudden death in the literature, the worst-case scenario of one case of sudden death gave an incident rate ratio of 1.63 (95% CI 0.04, 9.71). Although it was not the primary outcome of the study, following reports of suicide in the cohort the standardized mortality ratio (SMR) of suicide was calculated. Due to differences in the definition of suicide used for children and adults, patients were categorized into two age groups: 11–14 years and 15–21 years. The SMR for suicide for patients aged 11–14 years was 161.91 (95% CI 19.61, 584.88). The SMR for suicide for patients aged 15–21 years was 1.84 (95% CI 0.05, 10.25).

Conclusion: This study demonstrated no increase in the risk of sudden death associated with stimulants or atomoxetine. However, an increased risk of suicide was seen. Although we cannot exclude that the medications may

contribute to the increased risk of suicide, there are other factors such as depression and antisocial behaviour that frequently co-exist with ADHD, which can also predispose to teenage suicide. Clinicians should identify patients at increased risk of cardiovascular events and identify those patients at increased risk of suicide, particularly males with co-morbid conditions, and monitor them appropriately.

Background

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder defined by the 'core' signs of inattention, hyperactivity and impulsiveness. Using the broader *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) criteria,[1] it is estimated that ADHD affects between 2% and 9% of school-aged children, depending on the level of impairment used for the definition.[2] In the UK, methylphenidate, dexamfetamine and atomoxetine are licensed for the treatment of ADHD. The stimulants methylphenidate and dexamfetamine are sympathomimetic drugs structurally similar to endogenous catecholamines. These drugs are thought to act both in the CNS and peripherally by enhancing dopaminergic and noradrenergic transmission.[3] Atomoxetine, a non-stimulant, is a highly selective and potent inhibitor of the pre-synaptic noradrenaline (norepinephrine) transporter, without directly affecting the serotonin or dopamine transporters.[4] The most common adverse effects reported with the stimulants include sleep disturbances and appetite suppression. Cardiovascular effects have also been reported. Studies in children and adults taking stimulants and atomoxetine have shown minor clinical but statistically significant increases in blood pressure and pulse.[5-11] In February 2006, the Drug Safety and Risk Management Advisory Committee of the US FDA voted to recommend a 'black-box warning' describing the cardiovascular risks of stimulant drugs. The move followed reports of sudden deaths from stroke, heart attacks and high blood pressure in patients taking Adderall® (mixed amfetamine salts) and Ritalin® (methylphenidate).[12] The review included 19 cases of sudden death in children under 18 years and six cases of sudden death in adults from the FDA's Adverse Event Reporting System. In the paediatric population (1–18 years), they reported a rate of sudden death of 0.36 per million amfetamine prescriptions dispensed and 0.16 per million methylphenidate prescriptions dispensed. In the adult population (19+ years), the rate of sudden death reported was 0.53 per million amfetamine prescriptions dispensed and 0.07 per million methylphenidate prescriptions dispensed.[13] The black-box warning was not implemented; however, the FDA directed manufacturers of these products to revise product labelling for doctors to reflect their concerns. An additional part of this revised labelling process was the creation of a Patient Medication Guide for each individual product.[14]

The FDA and the Agency for Healthcare Research and Quality are collaborating in the largest study ever to examine the potential for increased risk of heart attack, stroke and other cardiovascular problems associated with medications used to treat ADHD.[15] However, the analysis is ongoing and, in the interim, concern still surrounds the issue of sudden death associated with ADHD medications. The aim of this study is to identify cases and causes of death in a cohort of patients prescribed stimulants and atomoxetine and to determine any association between these drugs and sudden death.

Patients and Methods

The data for this study was obtained from the UK General Practice Research Database (GPRD). The GPRD is a computerized database of anonymized longitudinal patient records maintained by

the Medicines and Healthcare products Regulatory Agency (MHRA). Currently it contains data for approximately 3 million active patients (~5% of the UK population) with a demographic distribution similar to the UK population. Validation studies show that the quality and completeness of the data is high.[16,17] The GPRD has been used to investigate the safety of the measles, mumps and rubella virus (MMR) vaccine[18] and the use of medicines in children.[19-23] Patients aged between 2 and 21 years during the study period (1 January 1993 to 30 June 2006) with at least one prescription for methylphenidate, dexamfetamine or atomoxetine were eligible for inclusion in the study. Patients were followed from the date of first prescription until whichever came first: date of death, transferred-out date, age >21 years, or end of the study period. Participants were censored if they had not died by the end of the study period, if they had transferred out of a practice or if a practice ceased to contribute data to the database. (Censoring arises when a patient has not yet experienced the relevant outcome, in this case death, before the end of the study follow-up.[24])

Once a general practitioner (GP) has been given notice of a patient death, they can enter a Read code (adopted by the UK Department of Health for use in general practice) or Oxford Medical Information System (OXMIS) code indicating a death category including 'Statement of Death' in the patient's medical record. GPs also have the option of using a structured data area to enter specific information on death administration or cause of death, while the third way of recording death in the GPRD is through recording the reason why a patient transferred out of a practice as death. Cases of death were identified by screening patients' medical records using the above three methods. This three-staged method allowed the identification of cases of death of all causes and was not restricted to cases of sudden death alone. The same method has been used by a UK MHRA-funded project to investigate the mortality rate of children prescribed antiepileptic drugs.[25]

Following identification of cases, a questionnaire was sent via the GPRD to the patients' family doctor to validate cases of death and to ascertain additional information including date of death, cause of death and other co-morbidities.

Sudden death was defined according to the WHO definition, which includes instantaneous death and all deaths occurring within 24 hours of an acute collapse.[26] Sudden death does not include cases such as suicide, homicide or other causes of unnatural death such as drowning or poisoning. The cause of death given by the GP as stated in the questionnaire was accepted as the true cause of death.

Using a method described by Wren et al.,[27] death was classified into one of five categories:

- death (not sudden) from known medical conditions;
- unnatural deaths (including homicide, suicide, drowning, poisoning and all other violent deaths);
- sudden deaths attributed to known pre-existing conditions;
- unexpected sudden deaths attributed to a natural cause discovered at autopsy;
- unexpected sudden deaths that remained unexplained after autopsy.

Crude and standardized mortality ratios (SMRs) were calculated on all cases of death, the latter using population data from the United Kingdom Office for National Statistics (ONS). SMR was defined as the ratio of the observed versus the expected number of deaths, with adjustment for differences in age distribution and sex, between the study cohort and the general population.[28] This indirect method of standardization is robust if numbers of events per stratum are sparse in the study population.

Fortunately, sudden death in children is rare, with a reported incidence of 0.8–6.2 cases/100 000 population per year.[29] For comparison purposes, we chose a rate of sudden death obtained from a study that was similar to the present study in terms of demographics of the population and the country in which the study was conducted. The study by Wren et al.[27] estimated a rate of sudden death of 3.3/100 000 per year. We performed incident rate ratio calculations (ratio of the incidence rate of sudden death in those exposed to the study drugs compared with a reference population) using poisson exact methods to handle small event numbers.[28] Although it was not the primary outcome

of the study, following reports of suicides in the cohort, we examined the rate of suicide and compared it with rates of suicide in the general population, again using data from the ONS. The algorithm used to determine cases of death was constructed so as to facilitate the examination of cases from all causes and so enabled us to examine not only cases of sudden death, but also cases of completed suicide. We did not include cases of attempted suicide or suicidal ideation.

The ONS defines suicide differently for children and adults; in adults and young people aged 15 years and over, the suicide figures include those deaths from intentional self-harm and those from 'injury or poisoning of undetermined intent' whereas in children under 15 years, deaths from injury or poisoning of undetermined intent are not included when examining suicide (intentional self-harm). Therefore, the cases of suicide in the drug cohort have been classified into two age categories: under 15 years, and 15 years and over. As there were no events in either the study population or the general population in children aged <11 years, the age categories were further refined to include children aged 11–14 years, and adolescents and young adults aged 15–21 years. Data were analysed using Stata/SE 9.1 for Windows (Stata Corp LP, College Station, TX, USA).

Ethical Approval

Ethical approval for the project was granted by the Independent Scientific Advisory Committee for MHRA database research. Although the GPRD is an anonymized database, the ethics committee requested that additional steps were taken to protect the anonymity of the small numbers of cases identified; therefore, certain patient characteristics, including age, sex and date of death have not been reported in this study. The patients' ages were categorized into the following groups: age 2–7, 8–15 and 16–21 years.

Results

The sample size for the defined cohort was 18 637 patient-years (n = 5351 patients). From

Table I. Cases and details of death in a cohort of patients prescribed methylphenidate, dexamfetamine and atomoxetine between 1993 and 2006 as reported by the patient's general practitioner (GP)

Patient	Age range (y)	Suspect drug	Active prescription	Cause of death	Co-morbid disorders	Death category[a]
1	16–21	Methylphenidate	No	Overdose, unknown intent	Anxiety/insomnia	Unnatural death
2	16–21	Methylphenidate	No	Not known	Depression	Not determined[b]
3	16–21	Methylphenidate	No	Stab wounds	Not known	Unnatural death
4	8–15	Dexamfetamine	Yes	Pancreatitis	Patient had severe epilepsy and was receiving a number of medications for epilepsy, including sodium valproate, lamotrigine and ethosuximide	Death (not sudden) from a known medical condition
5	8–15	Methylphenidate	Yes	Suicide	No	Unnatural death
6	8–15	Methylphenidate	Yes	Suicide	Aggressive personality	Unnatural death
7	2–7	Dexamfetamine	Yes	Brain tumour	No	Death (not sudden) from a known medical condition

a Classified by members of the study group following analysis of questionnaires.

b This patient did not have a reason of death in the General Practice Research Database medical records and it was not known by the GP. This patient had a history of depression and attention-deficit hyperactivity disorder and did not have an active prescription for methylphenidate at the time of death. The patient had received only one prescription for methylphenidate, approximately 5 months prior to death. The duration of this prescription was 14 days. The patient did not have any other recorded medical conditions or medications prescribed. An attempt was made to obtain the death certificate for this patient to ascertain cause of death; however, due to a number of issues with the patient's GP practice, it was not possible to do so. Therefore, it was not possible to determine whether this was a case of sudden death.

Table II. Suicide in young people from 1993 to 2006 in the General Practice Research Database (GPRD) cohort and the general population (using Office for National Statistics data)

	Age 11–14 y[a]		Age 15–21 y[b]	
	GPRD cohort	general population	GPRD cohort	general population
Number of cases of suicide	2	56	1	4142
Population (patient-years)	7543	37 234 000	5824	63 130 526
Incident rate of suicide per 100 000 patient-years	26.5	0.15	17.2	6.6

a SMR adjusted for sex = 161.91 (95% CI 19.61, 584.88).

b SMR adjusted for sex = 1.84 (95% CI 0.05, 10.25).

SMR = standardized mortality ratio.

this, seven patients died. Questionnaires were sent to the respective family doctors with a response rate of 100%. Table I contains the details of the seven cases of death identified.

The crude mortality rate was calculated based on all cases of death (n = 7) and was 37.6 per 100 000 patient-years.

Population and mortality data for the general public was obtained from the ONS using data for the mid-year of the study (1998). The SMR, defined as the ratio of observed deaths in the study cohort to the number of deaths expected, was calculated using the indirect method. The SMR was stratified by age and sex; however, only total figures are reported due to the ethical restrictions discussed in the previous section. The SMR was 1.44 (95% CI 0.58, 2.96), indicating no difference was detected in mortality rates between the general population and study cohort when applying a 5% two-sided significance level.

For those patients with a confirmed cause of death (n = 6), none were considered to be cases of sudden death.

Incident rate ratios were calculated to both include and exclude the one unconfirmed case of death.

The best-case scenario would be that none of the cases (0/7) were cases of sudden death. Comparing this rate with the rate of sudden death in the literature[27] gave an incident rate ratio of 0 (95% CI 0, 6.35). The worst-case scenario was that the one unconfirmed case was a case of sudden death (1/7). This gave an incident rate ratio of 1.63 (95% CI 0.04, 9.71).

Suicide (two patients) and overdose of unknown intent (one patient) were listed as the causes of deaths in three of the seven patients. This data was compared to data on suicide in the general population obtained from the ONS (table II). The SMR for suicide for children aged 11–14 years was 161.91 (95% CI 19.61, 584.88). For young people aged 15–21 years, the SMR for suicide was 1.84 (95% CI 0.05, 10.25) [table II].

Discussion

The FDA concluded in their report that due to limitations in the information available on the cases and the methods used to obtain the data, it was not possible to make a direct comparison between the reported rates of sudden death during stimulant therapy with background rates of sudden death in the general population. It also acknowledged that using a spontaneous reporting system, under-reporting was likely to underestimate the incidence of these events.[13] In the UK, from the period July 1963 to June 2006, there were two cases of sudden death associated with methylphenidate, dexamfetamine and atomoxetine reported to the spontaneous reporting system, the Yellow Card System.[30]

In this study, it was possible to accurately identify and validate cases of death from a defined cohort of patients receiving stimulant therapy. In total, seven cases of death were identified from a cohort of 18 637 patient-years. Using this cohort of patients, it was not possible to demonstrate any increase in the risk of sudden death when compared with the rate of sudden death described in the literature.

Though the medications used in the treatment of ADHD could theoretically set in motion a

cascade of biological events that may result in sudden death, we have demonstrated in this study that the risk of sudden death is no higher than is seen in the general population. In 2008, the American Heart Association (AHA) provided a statement on the cardiovascular monitoring of children and adolescents with ADHD.[31] They suggest that before starting treatment a careful history should be taken by clinicians to determine if there is a family history of long-QT syndrome or other causes of sudden, unexplained death, or a personal history of symptoms such as palpitations, syncope, near syncope or chest pain. In addition, a full medication history should be obtained, along with baseline blood pressure, pulse measurements and full physical examination. At follow-up visits, patients should be asked about the addition of any drugs and the occurrence of any of the above symptoms. Again, blood pressure and pulse should be monitored periodically throughout treatment. Although the AHA recognize the absence of clinical data on the use of ECGs prior to stimulant initiation, they state that ''it can be useful to add an ECG, which may increase the likelihood of identifying significant cardiac conditions''.[31] Whilst recommending a full history and physical assessment prior to stimulant initiation, the routine use of ECGs before beginning treatment is not supported by groups such as the American Academy of Pediatrics.[32]

In light of the results obtained, further analysis was conducted into the rate of suicide amongst the cohort. The SMR for suicide among younger children (aged ≤14 years) showed that those in the ADHD cohort were 162-fold more likely to commit suicide in comparison with the general population at 1% two-sided significance level.

The SMR for suicide in older children and young adults was 1.84, although 95% confidence intervals indicated that there was no statistically significant difference in suicide rates between the ADHD cohort and the general population.

When looking at cases of suicide, it is important not only to consider the medications but also the condition they are being used to treat. An association between ADHD and suicide has been demonstrated for younger males, although the evidence for any direct or independent link was modest. It is thought that the increase occurs via the increase in the severity of co-morbid conditions, in particular bipolar disorder, depression and conduct disorders.[33] Therefore, although we cannot exclude the possibility that the medications may contribute to the increased risk, there are other factors such as depression and antisocial behaviour, which frequently co-exist with ADHD, which can also predispose to teenage suicide.[33] It must also be borne in mind that untreated ADHD increases the risk of substance abuse (tobacco, alcohol and drugs) and being involved in motor vehicle accidents, both of which significantly increase the risk of morbidity and mortality.[34-38]

Strengths and Limitations

The GPRD is a good source of data for this study as it contains high quality longitudinal data on a large population of general practice patients. Also, it is a requirement for contributing practices that a transferred-out reason and date is accurately recorded for patients who have died. Furthermore, unlike many health systems in other countries, family doctors in the UK act as the gatekeeper to the secondary and tertiary healthcare system and so are almost always informed of the death of a patient occurring in hospital. If a patient dies outside of the hospital setting, then the family doctor is almost always involved in the issue of the death certificate. In addition, the verification service provided by the GPRD allows the researcher to confirm all cases of death and to obtain additional patient information. We are therefore confident that the methods utilized in this study have allowed us to accurately determine cases of death in a large cohort of patients taking ADHD drug treatment.

To our knowledge, with a sample size of 18 637 patient-years, this is one of the largest pharmacoepidemiological studies to examine the incidence of death of all causes and sudden death in patients taking medications used to treat ADHD. However, as mentioned, as sudden death in children is so rare, the present study would not have sufficient power to detect this event. As this is a pharmacoepidemiological study, we are

constrained by the size of the database; however, what this study does do is give assurance to clinicians and patients that the risk of sudden death in patients taking these stimulants and atomoxetine is extremely small and is unlikely to be any higher than the risk in the general population.

We have compared our rate of sudden death with a rate published in the literature by Wren et al.[27] The study reviewed all deaths at age 1–20 years in the North of England between 1985 and 1994, and reported a rate of sudden death of 3.3/100 000 per year. This figure may be an underestimation as the authors acknowledge that their definition of sudden death was more strict than the WHO definition of sudden death. Comparisons with population-based reports are very difficult as the methods used to gather data, the time when the study is conducted and the demographics of the populations can vary immensely between different reports. However, the comparator study was conducted in the same country as the present study and examined deaths in a population with a similar age range.

Conclusions

Clinicians, patients and parents should be provided with accurate information on the risks, benefits and adverse effects of methylphenidate, dexamfetamine and atomoxetine. In this study, it was not possible to demonstrate an increase in the risk of sudden death associated with methylphenidate, dexamfetamine or atomoxetine. Although it was not an initial aim of this study, an increase in the risk of suicide was observed, particularly in the younger teenager category. Clinicians should identify patients at increased risk for cardiovascular events and those patients at increased risk of suicide, particularly males with co-morbid conditions, and monitor them appropriately.

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