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Mortality in Children and Adolescents Prescribed Antipsychotic Medication

A Retrospective Cohort Study Using the UK General Practice Research Database

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Abstract

Background: Antipsychotic prescribing in children has risen in many countries; however, the safety of these agents in the young has not yet been fully established. Potentially fatal antipsychotic-related adverse events include cardiac complications and neuroleptic malignant syndrome.

Objective: The objective of this study was to investigate mortality in children and adolescents taking antipsychotic medication.

Methods: The General Practice Research Database (GPRD) was used as a data source for this study. Cases were identified from a cohort of patients previously studied. The study population encompassed all patients aged 18 years and under who received at least one prescription for an antipsychotic from 1 January 1992 to 31 December 2005. Patients were followed from the date of the first antipsychotic drug prescription until the earliest occurrence of a code of death, age >18 years or the end of the study period. Cases of death were identified by screening patients' medical records for clinical or referral events with events indicating death, or if a transferred-out patient has a 'transfer out reason' specified as 'death'. Confirmation of cases was carried out by examining individual patient profiles and from questionnaires sent to GPs. If necessary, the death certificates and/or post mortem reports were obtained by the source data verification service the GPRD provide. Once cases of death were identified, crude mortality rate (CMR) and standardized mortality ratio (SMR) were calculated. Baseline mortality rates were obtained from the Office for National Statistics. A modified WHO causality assessment was conducted to determine the likelihood of a relationship between the drug and an event of death.

Results: The cohort contained 2767 patients who received at least one antipsychotic prescription. There were 30 deceased cases in the cohort. The GP questionnaire response rate was 97%. Of the 30 cases, 24 were related to pre-existing medical conditions, including neoplastic diseases and HIV. After excluding these patients, six cases of death from 5963 person-years and 1958 treatment-years remained. The median age of death was 17 years (interquartile range 14–17.75). The overall CMR was 1.01 per 1000 person-years at risk (95% CI 0.20, 1.81) and SMR was 4.03 (95% CI 1.48, 8.76). Of the six cases, only one was deemed *possibly* associated with antipsychotic therapy, based on the causality assessment analysis conducted; CMR based on this case was 0.51 per 1000 treatment-years (95% CI 0.09, 2.89). The remaining five cases of death were *unlikely* to be associated with antipsychotic therapy.
Conclusions: Our study demonstrated an elevated SMR in patients exposed to antipsychotics. However, the elevated SMR was unlikely caused by antipsychotic treatment, but would suggest the possibility of inadequate management or poor control of patients' underlying medical conditions prior to death.

Background

Studies have shown an increase in the prescribing of antipsychotic medications in the paediatric population in many countries. In the US, a study by Cooper et al.[1] demonstrated a 2-fold increase in the number of new users of antipsychotics aged 2–18 years between 1996 and 2001 (from 23 to 45 users per 10 000 children). A 2-fold rise in antipsychotic medication use (2.1–4.2%) was also observed in Medicaid youths aged 6–17 years between 2001 and 2004; a more gradual increase in antipsychotic use was seen in privately insured youths between 1996 and 2006 (0.2–0.9%).[2] Another study in the US showed a 6-fold rise in the number of 'office-based visits by youth that included antipsychotic treatment' from 1993 to 2002.[3] In the Netherlands, there was a 54% increase in new users of antipsychotic medications (from 1.1 to 1.7 users per 1000 children) and a 2-fold increase in the prevalence of antipsychotics (from 1.6 to 3.4 users per 1000 children) between 1995 and 1999.[4] An increase in the prevalence of antipsychotic prescribing in the UK has also been reported, although not to the same extent as the US. In the UK, there was an almost 2-fold increase (from 0.39 to 0.77 per 1000 person-years) in the prevalence of antipsychotic prescribing from 1992 and 2005. However, during the same period the incidence (number of new patients taking antipsychotic medication) remained relatively stable (0.30–0.33 per 1000 person-years).[5] Possible reasons for the increasing trend of antipsychotic use include the availability of newer antipsychotic agents, the 'atypical antipsychotics', as well as a reported increase in the rate of psychiatric disorders in children, including non-schizophrenic disorders.[3,5]

Despite the evident increase in use, the safety profile of antipsychotic medications has not yet been fully established in the young. In the US, a number of antipsychotics are licensed for psychiatric conditions such as schizophrenia, bipolar disorders and irritability in autistic children;[6,7] however, in the UK, antipsychotic agents are mainly licensed for the treatment of psychotic conditions such as schizophrenia (risperidone is indicated for the short-term treatment of aggression in paediatric patients with conduct disorder with sub-average intellectual functioning).[8,9] Many studies have reported that the majority of these drugs are found to be used off-label or outside their product license in children and adolescents.[5,10] The newer generation or atypical antipsychotics were

developed in part to offer treatment with an improved safety profile over the first-generation typical antipsychotics; however, there have been reviews and meta-analyses suggesting that the atypical antipsychotics are associated with many of the same adverse effects being seen with the older generation drugs.[10,11] More importantly, the connection between the event of unexpected death and antipsychotic medication use has long been suspected.[12] Sudden death in patients taking antipsychotics is thought to be the result of cardiac complications; more specifically, arrhythmias as a result of prolongation of the QT interval, which in turn may lead to torsades de pointes and other cardiac arrhythmias.[13] Other serious and potentially fatal adverse drug reactions such as neuroleptic malignant syndrome have also been reported.[14]

We believe that the increase in use of antipsychotics for children and young people and the significant adverse effect profile merits careful investigation. The objective of this study was to investigate mortality in children and adolescents taking antipsychotic medication.

Methods

Data Source

Data for this study were obtained from the General Practice Research Database (GPRD). The history of the GPRD and validation of its data are described in more detail elsewhere.[15,16] Data from the GPRD are collected from anonymized patient records from participating general practitioners (GPs) in the UK. The GPRD currently contains over 35 million person-years of data from about 400 UK general practices. In 2009, the GPRD contained 793 636 registered patients aged 19 years and below.[17] The GPRD has been widely used to investigate the prescribing of medicines in children[18-21] as well as mortality in children receiving antiepileptic medication[22] and mortality in children receiving attention-deficit hyperactivity disorder (ADHD) medications.[23]

Data available from the GPRD include patient demographics, patient registration details, practice details, therapy records including medicines prescribed to patients, consultation details with a unique identifier for each consultation, clinical records, laboratory tests and referrals.

Ethics approval was granted by the former Scientific and Ethical Advisory Group of the GPRD, and the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Inclusion Criteria

The study population encompassed all patients aged 18 years and under between 1 January 1992 and 31 December 2005 who had received at least one prescription for an antipsychotic medication.[5] Patients had at least 1 year of research standard data available, an acceptable patient registration status, and sex was known.

Data Extraction

Cases were identified from a cohort of patients previously studied.[5] Patients in the cohort were followed from the date of the first antipsychotic drug prescribed until the earliest occurrence of a clinical code related to death, age >18 years or the end of the study period. To identify cases of death, an algorithm devised by GPRD was followed. The same algorithm was used in an MHRA-funded project to investigate mortality in children exposed to antiepileptic drugs[22] and in children exposed to ADHD medications.[23] Cases of death were identified by screening patients' medical records for clinical or referral events with a clinical code of 'death'. Cases were also identified if a patient had a 'transfer out reason' such as 'death', i.e. a patient was no longer registered with the practice due to death.

Confirmation of cases was carried out by examining individual patient profiles. Additional clinical information, including cause of death, the presence of co-morbid illnesses, exposure and indication of antipsychotics, as well as concurrent medication, was requested from the GP via questionnaires. If required, the death certificates and/or postmortem reports were obtained by the 'follow-up' and source data verification service provided by the GPRD. The verification service allows researchers to obtain additional informa-

tion to validate death. All patient identifiers were anonymized by the GPRD.

Data Analysis

Person-years of follow-up were defined as the date of the first prescription until the date of death, age >18 years or end of the study period. On the other hand, exposure was defined as the duration of time a subject was exposed to antipsychotic treatment. This was calculated by first determining the duration of prescriptions by dividing the quantity of drug prescribed by the daily dosage of the drug, which was obtained from the GPRD. For example, a patient who was prescribed 56 tablets with a daily dose of two tablets a day would have a prescription duration of 28 days. After prescription durations were calculated, the durations of treatment episodes were determined. Treatment episodes were defined as the duration of time when the patient was exposed to antipsychotic therapy based on the prescription durations. The following formula was used to calculate episode durations (equation 1):

$$\text{Episode duration} = E_{epis} - S_{epis} + L \qquad \text{(Eq. 1)}$$

where E_{epis} is episode end date, S_{epis} is episode start date and L is latency period of 30 days.

If a gap of >90 days was present between treatment episodes for a patient, then a treatment gap was presumed. Exposure was calculated as the sum of episode durations from the date of the first prescription until the end latency date, date of death or end of the study period. The end latency date was defined as the end of the episode duration date plus an additional 30 days. The latency period was added to the episode duration to allow for non-compliance, delay in drug dispensing, as well as half-life drug kinetics. The total duration of exposure was expressed as treatment-years.

Crude mortality rate (CMR) and standardized mortality ratio (SMR) were calculated.[24] Baseline mortality rates were obtained from population data from the Office for National Statistics (ONS). Mortality rates of 1998 (midpoint of the study) from the ONS were used as a reference year in the calculation. Mortality rates for the calculation of the SMR were based on the age groups 0–1 year, 2–5 years, 6–11 years and 12–18 years.

CMR was calculated using the following equation (equation 2):

$$\text{CMR} = \frac{N_c}{D} \times 1000 \qquad \text{(Eq. 2)}$$

where *Nc* is number of deaths in the cohort and *D* is total duration in person-years or treatment-years.

The SMR and the 95% confidence intervals (CI) were calculated. The SMR is the ratio of deaths observed in the study cohort to the number of deaths that would be expected during the follow-up period if the group in question had experienced the same age- and sex-specific rates of death as the general population.[24]

The expected number of deaths, *E*, was calculated using the following equation (equation 3):

$$E = M \times D \qquad \text{(Eq. 3)}$$

where *M* is mortality rate of the general population and *D* is total duration of follow-up in person-years.

The SMR was calculated using the following equation (equation 4):

$$SMR = \frac{N_c}{E} \qquad \text{(Eq. 4)}$$

where N_c is number of deaths in the cohort and *E* is number of deaths that would be expected.

Once all cases of death were confirmed, a causality assessment modified from the WHO-Uppsala Monitoring Centre (UMC) system for standardized case causality assessment[25] was carried out to determine the likelihood of a relationship between the drug and an event of death. As the investigated event of interest is death, the WHO-UMC system was modified to exclude the criteria for rechallenge. The event of death was considered not to have a plausible time-relationship if the event occurred more than 6 months after the last date of drug exposure.

The causality assessment was conducted by a consensus panel consisting of a research pharmacist (FR), paediatric pharmacoepidemiologist (ICKW), paediatric clinical pharmacologist (NC) and consultant child and adolescent psychiatrist (PB). Any disagreements between the panel

members were discussed until a consensus was reached among all members. Classification and criteria of the causality assessment is shown in table I.

Results

A total of 2767 patients who received at least one antipsychotic prescription contributing to 6007 person-years and 2041 treatment-years were previously identified.[5] The median exposure duration for all antipsychotic drugs was 86 days (interquartile range 53–226 days). From this cohort of patients, a total of 30 deceased patients were identified.

There was a 97% response rate from the questionnaires sent to the GPs. Additional verification was requested for three cases of death, and the death certificates were obtained for two of the three patients.

Upon investigating the causes of death in the 30 patients, it was found that 24 had a cause of death related to neoplasms (n = 17), AIDS (n = 1), genetic or inherited disorders (n = 5) and childhood dementia (n = 1). Consequently, all patients in the cohort who had clinical events related to these conditions, as well as other terminal illnesses, prior to their first prescription for an antipsychotic were then excluded in the analysis.

Table I. Categories used for the causality assessment for cases of death in the cohort

Causality term	Assessment criteria
Certain	Event of death with a plausible time relationship to drug intake
	Event cannot be explained by other disease or drugs
	Event definitive pharmacologically or phenomenologically
Probably/likely	Event of death with reasonable time relationship to drug intake
	Event unlikely to be attributed to other disease or drugs
Possible	Event of death with reasonable time relationship to drug intake
	Event could be possibly explained by disease or other drugs
Unlikely	Event of death with a time to drug intake that makes a relationship improbable, but not impossible
	Disease or other drugs provide plausible explanations

After the adjustment, there were six cases of death from 5963 person-years and 1958 treatment-years. There was an equal number of males (n = 3) and females (n = 3). The median age of death was 17 years (interquartile range 14–17.75). After adjusting for pre-existing medical conditions, the overall CMR was 1.01 per 1000 person-years at risk (95% CI 0.20, 1.81). The adjusted SMR was 4.03 (95% CI 1.48, 8.76).

Causality Assessment on the Deceased Patients

Using the modified WHO-UMC system for standardized case causality assessment, a causality assessment analysis was conducted on the remaining six cases of death. Information on these patients is shown in table II.

Only one of the six cases of death was *possibly* associated with antipsychotic medication (patient 21). The cause of death for this patient was listed as epilepsy-based on the death certificate obtained. As antipsychotic medications can lower the seizure threshold and modify EEG discharge patterns,[26] it was concluded that the antipsychotic medication in question, thioridazine, was *possibly* associated with the event of death in this subject. A more detailed conclusion was not possible as the subject had pre-existing epilepsy and information on drug withdrawal was not sufficiently clear.

Consequently, results on causality assessment demonstrated that antipsychotic therapy was *possibly* associated with the event of death in only one patient (patient 21). Based on this, and after adjusting for person-years of treatment exposure, the CMR was 0.51 cases per 1000 treatment-years (95% CI 0.09, 2.89 cases per 1000 treatment-years at risk).

Discussion

Mortality Rates

In recent years, much attention has been given to mortality associated with drug treatments, including antiepileptics, stimulants and antibiotics, in the paediatric population.[22,23,27,28] To our knowledge, this is the largest UK paediatric cohort that has been used to investigate mortality

Table II. Causality assessment on the six deceased patients

Patient no.	Sex	Age at death (y)	Cause of death	Antipsychotic and other CNS-acting drugs	Causality assessment	Outcome[a]
12	Female	18	From GP questionnaire: drug overdose (morphine sulphate)	Not exposed to any antipsychotics or other CNS-acting drugs at the time of death	Subject was not exposed to antipsychotic therapy when the event occurred, demonstrating a poor time relationship between drug intake and the event. The last prescription for an antipsychotic agent, chlorpromazine, was given more than 6 mo prior to the date of death Subject also suffered from depression. Suicidal ideation was first recorded approximately 3 wk before the date of death. These conditions provide a more plausible explanation of the circumstances of death	Antipsychotic drug therefore *unlikely* to have contributed to the cause of death in this case
13	Female	6	From GP questionnaire: undiagnosed progressive neurological condition	Chlorpromazine	Subject was exposed to antipsychotic therapy when the event occurred, indicating a reasonable time relationship between drug intake and the event of death. Subject also suffered from pre-existing dyskinetic cerebral palsy. Subject's cause of death is not phenomenologically or pharmacologically related to antipsychotic medication	Antipsychotic drug therefore *unlikely* to have contributed to the cause of death in this case
16	Male	17	From GP questionnaire: unknown; self-harm From death certificate: multiple injuries	Not exposed to any antipsychotic agents at the time of death Subject was taking fluoxetine	Subject was not exposed to antipsychotic therapy when the event occurred, demonstrating a poor time relationship between drug intake and the event. The last prescription for an antipsychotic, olanzapine, was given more than 6 mo prior to the date of death. Subject also suffered from depression and was on fluoxetine therapy, which provides a more plausible explanation of the circumstances of death	Antipsychotic drug therefore *unlikely* to have contributed to the cause of death in this case
21	Male	13	From death certificate: epilepsy	Thioridazine	Subject was exposed to antipsychotic therapy when the event occurred, indicating a reasonable time relationship between drug intake and the event. Subject also suffered from seizures, even prior to starting antipsychotic treatment. However, the subject was not exposed to any antiepileptic agent at the time of death (the last antiepileptic agent, carbamazepine, was prescribed more than 2 y before the date of death). Thioridazine has been known to lower the threshold of seizures	Antipsychotic drug therefore *possibly* to have contributed to the cause of death in this case
27	Male	18	From death certificate: (1a) acute peritonitis; (1b) perforation of small bowel by chicken bone; (2) Downs syndrome	Risperidone	Subject was exposed to antipsychotic therapy when the event occurred, indicating a reasonable time relationship between drug intake and the event. Subject's cause of death is not phenomenologically or pharmacologically related to antipsychotic medication	Antipsychotic drug therefore *unlikely* to have contributed to the cause of death in this case
30	Female	17	From GP questionnaire: Creutzfeldt-Jakob disease	Not exposed at the time of death	Subject was not exposed to antipsychotic therapy when the event occurred, demonstrating a poor time relationship between drug intake and the event. Subject's cause of death is not phenomenologically or pharmacologically related to antipsychotic medication	Antipsychotic drug therefore *unlikely* to have contributed to the cause of death in this case

a Please see table I for further details on causality assessment.

GP = general practitioner.

related to antipsychotic medication. The SMR demonstrated in our study (SMR 4.03; 95% CI 1.48, 8.76) was found to be higher compared with subjects receiving stimulant medication. McCarthy et al.[23] reported an SMR of 1.44 (95% CI 0.58, 2.96) in the cohort of paediatric subjects who received at least one prescription for methylphenidate, dexamfetamine or atomoxetine in the treatment of ADHD. On the other hand, the SMR demonstrated in our study is much lower compared with the study conducted by Ackers et al.,[22] who investigated mortality rates in paediatric patients exposed to antiepileptic therapy. The SMR reported by this study was 22.4 (95% CI 18.9, 26.2).

Based on the six cases of death identified (after adjusting for pre-existing medical conditions), the CMR was 1.01 per 1000 person-years at risk (95% CI 0.20, 1.81); however, this does not take into account exposure to antipsychotic therapy, or causality. Only three of the six subjects were exposed to antipsychotic therapy at the time of death, revealing a CMR of 1.53 per 1000 treatment-years. Additionally, because of the very low number of cases identified in our study, we were unable to show a statistically valid relationship to duration of exposure. While the risk of sudden cardiac death in adults taking antipsychotic agents may be dose-related, Ray et al.[29] stated that the effect of duration of treatment on risk of cardiac death has not been adequately tested. Studies of mortality and physical morbidity among adult psychiatric patients treated with antipsychotics are confounded by lifestyle issues associated with psychiatric disorder.[30] With regard to paediatric populations, it is unlikely that child psychiatric patients show the same degree of lifestyle risk factors such as exposure to nicotine use or lack of exercise and poor diet, which confound the adult studies. Nevertheless, it is possible that a longer duration of antipsychotic drug exposure might be associated with higher mortality, especially in the later years of life. For example, there is good evidence that adolescent patients treated with atypical antipsychotics may develop adverse effects, such as obesity, which are associated with later risk of cardiac disease and diabetes mellitus, but are unlikely to be a significant cause of death in the short term.[10] These issues could only be tested in studies of cohorts where treatment with antipsychotics straddles adolescence and early adulthood.

Causality Assessments

Our results yielded an elevated SMR of 4.03 (95% CI 1.48, 8.76), suggesting a higher mortality rate in the study cohort of patients who received antipsychotic treatment compared with the general paediatric population. Nevertheless, it was unlikely that the use of prescribed antipsychotic drugs was associated with the event of death in the majority of these identified cases. There was only one patient (patient 21) where the causality assessment concluded that it was *possible* for the antipsychotic medication to be associated with the event of death. This patient was exposed to thioridazine at the time of death, providing a plausible temporal relationship between the drug and the event. The patient was suffering from seizures approximately 2 years prior to receiving his first prescription for thioridazine, and died approximately 3 weeks after receiving his last prescription. The cause of death, as stated on the coroner's certificate, was epilepsy. Antipsychotic medications, including thioridazine, have been known to lower the seizure threshold and induce EEG discharge patterns that are related to epileptic seizures.[26,31] It has also been suggested that children and adolescents exposed to antipsychotic therapy have a significantly higher risk ratio for developing convulsions compared with that of adult patients.[32] Patients suffering from epilepsy, including those from the paediatric population, have a higher rate of mortality compared with the general population.[22] The cause of death for this patient could be explained by the patients' pre-existing seizures or any of the complications of epilepsy previously mentioned; however, the possibility that adverse effects of thioridazine contributed to the cause of death cannot be overlooked.

Although the majority of identified cases of death in this study were unlikely to be associated with antipsychotic therapy, the elevated SMR could be due to the very severe and complex nature of the underlying primary illness and/or to inadequate

management of patients' underlying medical conditions prior to death. This includes the management of diseases such as epilepsy and depression.

Limitations

Although the study population involved over 6000 patient-years of follow-up time and therefore is currently one of the biggest pharmacovigilance studies for atypical antipsychotics in children, it is still relatively small when compared with studies conducted in adults. Unfortunately, this is a common problem when conducting safety studies in the paediatric population. Additionally, as the primary source of data for this study was the GPRD, patients' compliance with prescribed antipsychotic therapy cannot be determined.

A confounding factor when investigating the association of mortality in patients taking antipsychotic medication is that patients with psychiatric disorders already suffer from an increase in mortality compared with the general population.[33,34] This is true even for patients who are not exposed to antipsychotic medication.[35,36] As previously discussed, there is a possibility of an increased risk of mortality with longer durations of exposure to antipsychotic therapy. However, we were unable to determine the long-term mortality risk in the study cohort as the median exposure duration was only 86 days (interquartile range 53–226 days).

Furthermore, to reduce possible limitations by relying solely on an epidemiological approach, we also used a method of clinical assessment using causality assessment analyses. The causality assessment was conducted by a multidisciplinary team and a standard method adapted from the WHO was used. This was to minimize any possible subjectivity, bias and misinterpretation of analyses.

Conclusions

Our study demonstrated an elevated SMR in the cohort of young patients receiving antipsychotics compared with the general population; however, it was unlikely that the antipsychotics were the cause of death in the majority of cases. The elevated SMR suggests the possibility of inadequate management or poor control of patients' underlying medical conditions prior to death.

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Contributors: Ian C.K. Wong, Fariz A. Rani and Macey L. Murray conceived the idea of the study. All authors were involved in the study design. Fariz A. Rani, Patrick Byrne, Noel Cranswick and Ian C.K. Wong analysed the data. All authors were involved in the interpretation of the data, had full access to the study data and take responsibility for the integrity of the data and accuracy of the data analysis. All authors drafted, revised and approved the final manuscript. Ian C.K. Wong is the guarantor.

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