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Mortality Rates and Causes of Death in Children with Epilepsy Prescribed Antiepileptic Drugs

A Retrospective Cohort Study using the UK General Practice Research Database

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Abstract

Background: Patients with epilepsy, including children, have an increased risk of mortality compared with the general population. Antiepileptic drugs (AEDs) were the most frequent class of drugs reported in a study looking at fatal suspected adverse drug reactions in children in the UK.

Objective: The objective of the study was to identify cases and causes of death in a paediatric patient cohort prescribed AEDs with an associated epilepsy diagnosis.

Methods: This was a retrospective cohort study supplemented with general practitioner-completed questionnaires, post-mortem reports and death certificates. The setting was UK primary care practices contributing to the General Practice Research Database. Participants were children and adolescents aged 0–18 years prescribed AEDs between 1993 and 2005. Causality assessment was undertaken by a consensus panel comprising paediatric specialists in neuropathology, neurology, neuropsychiatry, paediatric epilepsy, pharmacoepidemiology and pharmacy to determine crude mortality rate (CMR) and standardized mortality ratios (SMRs), and the likelihood of an association between AED(s) and the event of death.

Results: There were 6190 subjects in the cohort (contributing 26 890 person-years of data), of whom 151 died. Median age at death was 8.0 years. CMR was 56.2 per 10 000 person-years and the SMR was 22.4 (95% CI 18.9, 26.2).

The majority of deceased subjects had severe underlying disorders. Death was attributable to epilepsy in 18 subjects; in 9 the cause of death was sudden unexpected death in epilepsy (SUDEP) [3.3 per 10 000 person-years (95% CI 1.5, 6.4)]. AEDs were probably (n = 2) or possibly (n = 3) associated causally with death in five subjects. Two status epilepticus deaths were associated causally with AED withdrawal.

Conclusions: Children prescribed AEDs have an increased risk of mortality relative to the general population. Most of the deaths were in children with serious underlying disorders. A small number of SUDEP cases were identified. AEDs are not a major cause of death but in a small proportion of cases, a causal relationship between death and AEDs could not be excluded.

Background

Patients with epilepsy, including children, have an increased risk of mortality compared with the general population. Possible causes of death include a complication of epilepsy, e.g. drowning, trauma, aspiration of gastric contents, convulsive status epilepticus or sudden unexpected death in epilepsy (SUDEP); a complication of drug treatment; or a related underlying cause such as a brain tumour or neurodegenerative disorder.[1] A published review of mortality in paediatric epilepsy states that the standardized mortality ratio (SMR) for all children with epilepsy is reported to be 7.0–13.2, which is higher than the SMR of 2–3 reported for all-age population epilepsy studies.[1] Antiepileptic drugs (AEDs) were the most frequent class of drugs reported in a study looking at fatal suspected adverse drug reactions (ADRs) in children in the UK.[2] The report showed that hepatic failure is the major cause of fatal suspected ADRs to AEDs. Other fatal suspected ADRs such as bone marrow suppression, Stevens-Johnson syndrome, disseminated intravascular coagulation and pancreatitis have also been reported.[2]

The newer AEDs, such as lamotrigine, topiramate and levetiracetam, are increasingly being prescribed to children in the UK.[3] Mortality data with these newer AEDs is sparse and their risks and potential contributions to fatal outcomes are unknown. The objectives of this study were to (i) identify cases and causes of death in a cohort of paediatric patients who have been prescribed AEDs and have an associated diagnosis of epilepsy; (ii) perform a causality assessment to determine the likelihood of an association between the AED(s) and the event of death; and (iii) calculate crude mortality rate and SMRs.

Methods

Study Design

A cohort study using the General Practice Research Database (GPRD) was performed to identify the incidence and causes of death in subjects prescribed AEDs who had at least one medical record of epilepsy or seizure.

Data Source

The GPRD is one of the world's largest computerized databases, containing anonymized primary care records for approximately 3.6 million patients from over 430 general practices in the UK and representing approximately 5% of the UK population. In the UK, the majority of the population are registered with a general practitioner (GP) who is responsible for primary healthcare and specialist referrals. The demographic distribution of the population covered by the GPRD is broadly representative of the population of England and Wales.[4] The GPRD has the capability for conducting paediatric drug utilization and pharmacovigilance studies because of the large size of the database population.[5] Participating

GPs enter demographic details, clinical information and diagnoses, detailed prescription data, immunizations, hospital referrals, and clinical investigation results and tests in a standardized manner into their clinical computing systems.[5] Validation studies show quality and completeness of the data is high[4] and studies investigating paediatric drug prescribing using the GPRD are becoming well established.[6-8] The database has previously been used to investigate the SUDEP incidence rate in adults[9] and to study the mortality of adolescents and young adults with attention-deficit hyperactivity disorder who were prescribed stimulants.[10]

Selection of Subjects

The cohort of subjects was identified from a previous study that looked at the drug utilization of AEDs in children and adolescents.[3] Subjects aged <19 years, of known sex, who had been prescribed at least one AED (a list of drug codes is available in the Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A47) in the study period (January 1993–December 2005) and had an associated diagnosis of epilepsy or seizure were identified (a list of medical codes is available in the Supplemental Digital Content). The data were extracted in November 2006 to allow for a lag time to identify death. Subjects were excluded if they had a temporary registration status or if they had <1 year of research standard data (unless the subject was aged <1 years when the subject was included regardless of the amount of data available). Age classification was modified from the International Conference of Harmonization; pre-term neonates, neonates and infants were included as one group as dates of birth were unavailable from the database in order to protect patient anonymity. Our classification is children aged <2 years, children aged 2–11 years and adolescents aged 12–18 years.[11] All AED prescriptions were identified and grouped as new or conventional.[12] For this study vigabatrin, lamotrigine, topiramate, gabapentin, oxcarbazepine, levetiracetam, tiagabine, pregabalin and zonisamide were classified as 'new' AEDs, although some of these have been licensed in the UK for >10 years. 'Conventional' AEDs included phenytoin, phenobarbital (phenobarbitone), sodium valproate and carbamazepine. Subjects were grouped as receiving 'new', 'conventional' or 'both' AEDs ('both' implying that they received both new and conventional AEDs). The clinical outcome of interest in this study was cause of death. To identify cases of death, an algorithm devised by the GPRD was followed; this same method has been used previously.[10] Subjects who die whilst registered with a contributing general practice are generally assigned the appropriate deregistration status. Cases of death were identified if a subject had the deregistration status ('transfer out reason') specified as 'death'. Cases of death were also identified by screening subjects' medical records for clinical or referral events with a Read or Oxford Medical Information System code indicating a death category. Ethical approval was granted by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Data Extraction

Primary data, in the form of individual patient profiles and records from the GPRD, were extracted using the standard GPRD data tools and imported onto a local server. Secondary data were obtained, via the GPRD verification service, as GP-completed questionnaires (see Supplemental Digital Content 1), post-mortem reports or death certificates, and latest hospital letters/discharge summaries. The Office for National Statistics (ONS) was contacted for death certificates not supplied by the GPs. These were used to confirm death, identify cause of death, and obtain characteristics of subjects and their deaths.

Data Analysis

Demographic data on epilepsy, death, underlying disorders and AED for the cases of death were analysed using all primary (GPRD records) data and secondary data (GP questionnaires, post-mortem reports, death certificates and hospital discharge letters) where available, for all subjects who had died. A consensus method was used to categorize the causes of death based on the *International Classification of Diseases,*

10th edition (ICD-10).[13] The expert panel included a paediatric neuropathologist (W. Squier), paediatric neurologist (E. Hughes), paediatric neuropsychiatrist (F.M.C. Besag), paediatric pharmacoepidemiologist (I.C.K. Wong) and paediatric pharmacist (R. Ackers). The consensus panel also performed a causality assessment at a face-to-face meeting to assess ADRs using the WHO criteria (see Supplemental Digital Content 1).[14] The criteria were adapted to remove the category of 'certain' as it was not possible to 'rechallenge' treatment.

SUDEP was defined based on Nashef's definition (1997) and as used by the National Sentinel Clinical Audit of Epilepsy-Related Death as "Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicological or anatomic cause for death".[15,16] For subjects with no available post-mortem report, SUDEP could still be assigned as the cause of death following review of the available information. SUDEP was classified as 'probable' or 'possible'; the 'possible' cases were those in which, on balance, it was judged relatively likely that they could be attributable to another cause but in which the possibility of SUDEP could not be excluded.

The Crude Mortality Rate (CMR) and SMR with 95% CIs were calculated. The SMR is the ratio of deaths observed in the study cohort to the number that would be expected during the same period based on age- and sex-specific strata of the general population.[17] UK general population annual mortality rates were obtained from ONS.

Results

A total of 6190 cohort subjects (3343 males [54%]), contributing 26 890 person-years, were examined. Within this cohort, 162 subjects had a death code and/or a transferred-out reason of death; questionnaires and secondary data were requested for these subjects. Following review of the secondary data, 11 subjects were excluded from the data analysis because of age of death >18 years (n = 4 subjects), no epilepsy diagnosis (n = 6) and subject presumed alive (n = 1). The secondary data response rate for the 151 subjects included in the data analysis was high, with 131 questionnaires (86.8%), 40 hospital letters/discharge summaries, 96 death certificates (63.6%) and 7 post-mortem reports.

Of the 151 subjects who died (86 males [57%]), the mean age of death was 8.7 years (median 8 years, interquartile range 3–15 years). Sixteen subjects died aged <2 years (11%), 76 subjects died aged 2–11 years (50%) and 59 subjects died aged 12–18 years (39%). The mean age of onset of epilepsy was 3.6 years (median 1 year, interquartile range 0–5.5 years) and only 10.6% of subjects developed epilepsy in adolescence. The cause of epilepsy from the questionnaires was prenatal brain damage or cerebral palsy in 55 subjects (36%), metabolic disorder in 15 subjects (10%), chromosomal disorder in 11 subjects (7%), brain tumour in 10 subjects (7%), other cause in 27 subjects (18%) and unknown in 33 subjects (22%). Table I shows the type of seizure or epilepsy that the subjects had, as identified from the questionnaire and additional information. Sodium valproate was the most commonly prescribed AED (n = 91 subjects), followed by carbamazepine (n = 65), vigabatrin (n = 45) and lamotrigine (n = 41); subjects could have been prescribed more than one AED.

The CMR was 56.2 per 10 000 person-years (95% CI 47.6, 65.8). Table II shows the CMR and number of deaths grouped by sex, age group and AED group. Underlying disorders were present in 123 subjects (81.5%), including neurological, metabolic, congenital and circulatory disorders. Causes of death were epilepsy related (but excluding SUDEP) in nine subjects (6.0%), and these resulted from status epilepticus (six subjects) or aspiration of gastric contents (three subjects). Two of the status epilepticus deaths were associated with AED withdrawal. SUDEP (as a specific cause of epilepsy-related death) occurred in nine subjects (6.0%), of which five were classified as probable SUDEP and four possible SUDEP. Non-epilepsy-related death occurred in 110 subjects (72.8%). After review of the post-mortem findings, GP questionnaires and hospital discharge summaries in four subjects, the cause of death as

Table I. Type of seizure or epilepsy and antiepileptic drug (AED) group prescribed for subjects who died during the study period

Type of seizure or epilepsy	No. of patients (%)	No. of patients for each AED group[a]		
		Conventional AED	New AED	Both AEDs
Generalized tonic-clonic	58 (38.4)	30	2	26
Myoclonic	7 (4.6)	1	2	4
Absence	1 (0.7)	1	0	0
Partial	2 (1.3)	0	0	2
Atonic	0	NA	NA	NA
Clonic	1 (0.7)	1	0	0
Tonic	1 (0.7)	1	0	0
Infantile spasms	5 (3. 3)	2	1	2
Lennox-Gastaut	0	NA	NA	NA
Other[b]	13 (8.6)	5	2	6
Unknown	63 (41.7)	34	4	25
Total	151 (100.0)	75	11	65

a AED group prescribed at any stage during management of the epilepsy.

b Combination of above seizure types (12 subjects) and epilepsia partialis continua (1 subject).

NA = not applicable.

stated on the death certificate was concluded to be inaccurate (table III). There was insufficient information to determine the cause of death in 23 subjects (15.2%). Figure 1 shows the causes of death grouped according to the ICD-10 classification.

For two subjects it was probable/likely that the AED had caused death, and for three subjects it was possible that death was AED-associated. It was unlikely that the AED was linked to death for 123 subjects (82%) and, because of lack of information, 23 subjects (15%) were unclassifiable. The presence of an underlying disorder and poor temporal relationship were key factors in separating the unlikely from the possible classifications. A reasonable temporal relationship would depend on the AED prescribed and the cause of death reported. If there was doubt about the reasonableness of the temporal relationship then the reactions were classified as possible rather than unlikely. Table IV gives details of the probable/likely and possible fatal ADRs. Possible classification was distinguished from probable/likely by the presence of other drugs or underlying disorders that could be responsible for death.

Table II. Crude mortality rates (CMRs) and number of deaths for subjects prescribed an antiepileptic drug (AED) by sex, age group and AED group

AED group	Sex	CMR per 1000 person-years (no. of deaths)			
		<2 years	2–11 years	12–18 years	0–18 years
Conventional AED	F	11.8 (1)	5.1 (17)	3.1 (13)	4.1 (31)
	M	16.5 (2)	5.2 (23)	3.4 (19)	4.3 (44)
	Total (F and M)	14.6 (3)	5.1 (40)	3.3 (32)	4.2 (75)
New AED	F	0.0 (0)	12.1 (3)	5.7 (3)	7.7 (6)
	M	141.2 (2)	7.8 (2)	3.2 (1)	8.5 (5)
	Total (F and M)	93.5 (2)	9.9 (5)	4.8 (4)	8.0 (11)
Both conventional and new AED	F	31.8 (2)	9.3 (16)	5.0 (10)	7.4 (28)
	M	121.3 (9)	7.2 (15)	7.2 (13)	9.3 (37)
	Total (F and M)	80.2 (11)	8.1 (31)	6.0 (23)	8.4 (65)
Total (conventional, new and both)	Total (F and M)	43.9 (16)	6.3 (76)	4.1 (59)	5.6 (151)

F = female; **M** = male.

Table III. Cases where the reported cause of death (CoD) was over-ridden by the consensus panel

Patient reference	Death certificate CoD			Questionnaire CoD	GPRD CoD	Underlying condition	Consensus panel CoD
	1a	1b	2				
15	Pneumonia	Ohtahara syndrome		Cardiac arrest – found by parents, cardiopulmonary resuscitation, accident and emergency	Pneumonia due to unspecified organism/cardiac arrest	Ohtahara syndrome	Possible SUDEP
17	Bronchopneumonia			Cause of morbidity/mortality ill-defined and unsure		No known underlying disorder	Possible SUDEP
84	Adult respiratory distress syndrome		Neurodegenerative disease		Status epilepticus	Motor sensory neuropathy	Status epilepticus
91	Epilepsy			Sudden collapse and death		No known underlying disorder	Probable SUDEP

GPRD = General Practice Research Database; **SUDEP** = sudden unexpected death in epilepsy.

The overall SMR was 22.4 (95% CI 18.9, 26.2). Table V shows the SMR by age group and sex. Females had a higher SMR than males; however, the difference was not significant. There were significant differences between the three age groups with SMRs being highest in children aged 2–11 years and lowest in those aged 12–18 years. Subjects prescribed 'new' or 'both' AEDs had

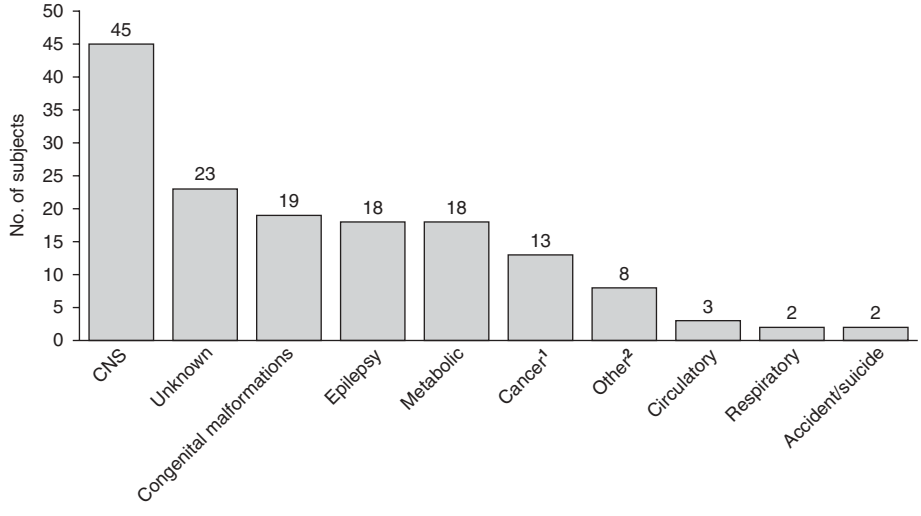

Fig. 1. Causes of death for subjects prescribed antiepileptic drug(s) classified by the *International Classification of Diseases, 10th edition*. CNS = all CNS causes excluding epilepsy-related causes (classified as 'epilepsy') and brain tumours (classified as 'cancer'). **1** Brain tumour (11 subjects), rhabdomyosarcoma (1 subject) and leukaemia (1 subject). **2** Liver failure (one subject), pancreatitis (two subjects), peritonitis (one subject), renal failure (two subjects) and septicaemia (two subjects). The 'epilepsy' causes were status epilepticus (six subjects), gastric aspiration (three subjects) and sudden unexpected death in epilepsy (nine subjects).

Table IV. Probable/likely and possible fatal adverse drug reactions with antiepileptic drugs (AEDs)

WHO classification	AED prescribed for epilepsy	Subject and age group (y)	Cause of death details	Comments
Probable/likely	Sodium valproate: first prescribed 4 y prior to death	F, 12–18	DC: acute pancreatitis with coroner verdict of misadventure GP: pancreatitis	Reasonable temporal relationship – pancreatitis has been reported to occur up to 14 y after sodium valproate initiation. Polytherapy with lamotrigine and acetazolamide. Sodium valproate most likely cause
Probable/likely	Sodium valproate: first prescribed 4 y prior to death	F, 2–11	DC: renal failure and pancreatitis with underlying cerebral palsy	Reasonable temporal relationship (see above). Previous AED treatment includes carbamazepine and vigabatrin. Underlying cerebral palsy and neurological complications
Possible	Carbamazepine: first prescribed 51 d prior to death	M, 2–11	DC: bronchopneumonia GP: cause of morbidity or mortality ill-defined and unsure Consensus panel classified cause of death as SUDEP	Relatively close temporal relationship. SUDEP provides a more plausible explanation
Possible	Topiramate: prescribed for 1 mo only over a 1-y period prior to death and then restarted 2 mo prior to death	M, 2–11	GP: sepsis and renal failure Underlying metabolic disorder (complex 1 mitochondrial respiratory chain enzyme deficiency) and cerebral palsy	Relatively close temporal relationship possibly suggested that the use of topiramate in subjects with this specific, very rare metabolic condition may expedite death. However, not known for topiramate to cause sepsis and renal failure.[a] Polytherapy with sodium valproate, lamotrigine and phenytoin
Possible	Topiramate: first prescribed 3 mo prior to death	F, 2–11	DC and GP: respiratory chain enzyme deficiency and epilepsia partialis continua	As above, relatively close temporal relationship possibly suggested that the use of topiramate in subjects with this specific, very rare metabolic condition may expedite death. However, terminal event is not known. Polytherapy with sodium valproate, carbamazepine and phenobarbital (phenobarbitone)

a No mention in GP records, hospital letters or DC of renal calculi, which is a known adverse effect of topiramate.

DC = death certificate; **F** = female; **GP** = general practitioner; **M** = male; **SUDEP** = sudden unexpected death in epilepsy.

higher SMRs (30.2 [95% CI 15.1, 54.1] and 32.5 [95% CI 25.1, 41.4]) than those prescribed 'conventional' AEDs (17.3 [95% CI 13.7, 21.7]).

Discussion

Key Findings

To our knowledge this is the first study to assess mortality in a large population-based cohort of children with epilepsy who were prescribed an AED.

The overall CMR of 56.2 per 10 000 person-years is similar to those reported in the literature which, for children with epilepsy, ranged from 27 to 62 per 10 000 person-years.[18-21] In our study, the AED-associated mortality rate of probable cases was 0.7 per 10 000 person-years (95% CI 0.1, 2.7). Yellow Card Scheme[2] data found that AEDs were the most frequently reported fatal suspected drug reactions in children; however, our population-based study gives some reassurance that AED-associated mortality is rare.

In two of the subjects who died because of status epilepticus, the GP questionnaire highlighted that the deaths were associated with AED withdrawal;

Table V. Standardized mortality ratios (SMRs) for subjects prescribed an antiepileptic drug by sex and age group

Age group (y)	Males [SMR (95% CI)]	Females [SMR (95% CI)]	Total [SMR (95% CI)]
<2	22.7 (13.0, 36.9)	17.0 (6.8, 35.0)	20.9 (13.2, 31.3)
2–11	37.5 (27.0, 50.7)	49.1 (33.6, 69.4)	42.4 (33.3, 53.2)
12–18	10.7 (7.1, 15.5)	19.5 (12.7, 28.5)	13.8 (10.4, 18.0)
0–18	19.4 (15.5, 23.9)	27.1 (20.9, 34.5)	22.4 (18.9, 26.2)

the overall incidence was 0.7 per 10 000 person-years (95% CI 0.1, 2.7). Although the absolute number is small, GPs and the consensus panel found a strong association between AED withdrawal and death that appears to confirm the importance of AED treatment in controlling seizures and helping to decrease the risk of mortality.

A high proportion of subjects in this study had an underlying disorder (81.5%), some of which are relatively rare but were observed in more than one child. The majority of subjects died from a cause that was non-epilepsy related (72.8%).

Over 60% of the subjects who died were prescribed more than one AED, suggesting they had more severe epilepsy and, hence, an increased risk of mortality. Only 7.3% were prescribed a new AED as monotherapy, which was to be expected with the more recent introduction of these drugs to the UK market.

SUDEP was classified as a probable cause of death in five (3.3%) subjects and possible cause of death in four (2.6%) subjects, which is equivalent to an incidence of 1.9 per 10 000 person-years (95% CI 0.6, 4.3) and 1.5 per 10 000 person-years (95% CI 0.4, 3.8), respectively. Four subjects who died from SUDEP had no known underlying disorder. Three of these subjects were treated with monotherapy, suggesting a milder form of epilepsy or better controlled epilepsy.

The causality assessment results suggest that AEDs are not a major cause of death in children with epilepsy but appear to be associated with a small number of cases. However, two issues need to be highlighted. First, there were two probable/likely cases of AED-associated mortality. First, pancreatitis in female subjects prescribed sodium valproate. Both subjects had been prescribed sodium valproate for 4 years prior to death. This was assumed a reasonable temporal relationship as pancreatitis has been reported in children exposed to sodium valproate and aged up to 7[22] and 14 years[23] prior to death. Studies in the literature also support that young people are more at risk.[23,24] Second, the two subjects with possible AED-associated deaths had a metabolic condition and were prescribed topiramate in the months prior to death. Both of these children were severely ill with debilitating metabolic and neurological problems; however, the possibility of topiramate expediting death in these children needs to be considered. Further details of these cases are available but cannot be reported as the research team deemed it inappropriate to ask for consent from the parents in order to publish these details; however, our final report was provided to the MHRA (the regulatory authority and funder of the study).

The SMRs for the different age groups show statistically significant differences, with children aged 2–11 years having a much higher SMR than infants and adolescents. This is probably due to the lower mortality rate in the general population (the denominator) for this age group. The SMRs for the different AED groups show that subjects prescribed a new AED were at increased risk of mortality. These differences are not significant and the reason for the difference cannot be determined because of the small number of subjects prescribed a new AED (11 subjects).

Strengths and Limitations

A previous study has concluded death certificates are not an effective way to study the rate of mortality in epilepsy.[25] In contrast to the previous study,[25] our study did not use death certificates to identify cases. Death certificates were used to 'confirm' death and to assist in determining the cause of death in conjunction with the GPRD data, GP questionnaires, hospital information and post-mortem reports. The combination of data from the different sources should increase the accuracy of the results.

A high response rate for secondary data was achieved, with 86.8% for GP questionnaires. Death certificates and post-mortem reports were unavailable, and the GP questionnaires had insufficient information for the 23 subjects (15.2%) who were classified with a cause of death as 'unknown'; there was insufficient information to determine the cause of death. It is unlikely that these subjects died from SUDEP or were AED-associated as they are more likely to have had a post-mortem and consequently to be well documented and remembered.

Similar to other mortality studies in patients with epilepsy, we were unable to identify a suitable comparator population. A comparator population of children with untreated epilepsies or those treated with AEDs for other indications was deemed to be inappropriate because of the confounding factor of severity of epilepsy. Because no fully matched comparator population was available, SMRs were used. Previously published epilepsy-related mortality studies have used a similar method of calculating SMR to ours,[18,19,26,27] which supports the validity of our chosen method.

The GPRD only contains therapy records from primary care. However, in the UK, epilepsy diagnosis is made by specialists in secondary care and treatment is usually continued by GPs in primary care.[28] The GPRD contains prescribing data so the results cannot determine whether the prescriptions for AEDs were dispensed or whether the subjects were compliant with the medication; this is a common limitation of automated databases.[5] Furthermore, the dose of AEDs could not be fully investigated as many of the GP records stated "as directed".

Comparisons of the AED-associated mortality rate cannot be made with that in the literature as no other paediatric studies have assessed whether AEDs can cause or influence death in children with epilepsy.

The majority of subjects died from a non-epilepsy-related cause; this is similar to what has been reported in the literature. Berg and colleagues[18] found that the underlying cause of epilepsy and complications related to these underlying disorders were the main causes of death. The Dutch Study of Epilepsy in Childhood showed that respiratory insufficiency and infection were the main causes of death.[19] Likewise, in a Canadian study the majority of subjects died from pneumonia and infection as well as circulatory problems.[26] Children with epilepsy in Victoria, Australia, were more likely to die from pneumonia and underlying disorders than causes directly attributable to epilepsy.[20] A previous UK study reported that more children died because of epilepsy-related causes, including status epilepticus and SUDEP.[27] However, this study was conducted in a specialist school for children with severe epilepsy and learning difficulties, implying that mortality rates and causes of death cannot be directly compared with those in the present population-based cohort study.

Four percent of subjects in our cohort died because of status epilepticus. In previous studies, the number of children who have died from status epilepticus varied from 0% to 14% of the deceased subjects.[18,19,26,27,29] The rate of SUDEP in children reported in the literature ranges from 1.1 per 10 000 person-years to 34 per 10 000 person-years;[20,26,27,30] our rate of 3.3 per 10 000 person-years is in line with these reported figures.

Eleven subjects from our deceased subject cohort were prescribed a new AED as monotherapy. The licensing for monotherapy of the new AEDs is restricted in children, which would further reduce the number of subjects prescribed only a new AED. Furthermore, the National Institute for Health and Clinical Excellence (NICE) guidance states that the newer AEDs are recommended in children who have not benefited from conventional AED treatment or if conventional AEDs are not suitable.[12] Sodium valproate and carbamazepine were the most commonly prescribed AEDs, which corresponds to the prescribing trends of AEDs shown in a recent UK study.[3] A high proportion of subjects were prescribed vigabatrin (29.8%), resulting in it being the third most commonly prescribed AED in the deceased patients of this study and the most common newer AED. Vigabatrin is now only licensed for the treatment of infantile spasms as monotherapy and as an adjunct for partial seizures.[31] Use of this drug has decreased following the discovery of associated visual field defects.[32,33] Its high rate of use in this group is likely to reflect the severity of the epilepsy. It is likely that some of the differences observed between the newer and older AEDs were because the newer AEDs were mainly prescribed to individuals with more difficult to control epilepsy that had not responded to the older AEDs. This implies that the patients on newer AEDs might have had more severe epilepsy. Because of the non-specific epilepsy clinical codes in the GP records it was not possible to verify which AEDs were being used to treat the different classifications of seizure type and epilepsy for >6000 cases.

Our finding of SUDEP as the cause of death in three subjects treated with monotherapy and without other underlying disorders apart from the epilepsy is of particular concern. Parents of children with epilepsy and clinicians treating these children need to be aware that SUDEP is possible, even in children with no underlying disorders, infrequent seizures and established AED treatment, but that the risk is very low. Langan et al.[34] reported that no treatment was a risk factor in a case-control study of SUDEP. Our study only included patients with pharmacological treatment; hence, we are unable to investigate whether no treatment is a risk factor. Nevertheless, appropriate counselling needs to be given to parents and carers, both at epilepsy diagnosis and throughout the childhood years.

A high percentage of children who die have an underlying disorder. Further work is urgently needed to improve the treatment of these children to reduce the mortality rate.

Conclusions

The majority of subjects who died had underlying severe neurological, metabolic or congenital disorders. The cause of death was attributable to epilepsy in 18 of the 151 subjects. Nine of the 18 epilepsy deaths were attributed to SUDEP (rate of 3.3 per 10 000 person-years) and four of these subjects had no identified underlying disorder. The AEDs were probably (n = 2) or possibly (n = 3) associated with death in only five subjects. Furthermore, two status epilepticus deaths were associated with AED withdrawal; the results suggest that AEDs are not a major cause of death, but in a small proportion of cases a causal relationship between death and AEDs could not be excluded. As the use of new AEDs in children increases, the risk of mortality needs to be continually reassessed.

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Contributors: Ian C.K. Wong, Frank M.C. Besag, Ruth Ackers and Macey L. Murray conceived the idea of the study. All authors were involved in the study design. Ruth Ackers and Ian C.K. Wong analysed the data, and Ruth Ackers, Frank M.C. Besag, Elaine Hughes, Waney Squier and Ian C.K. Wong interpreted the data. All authors had full access to the study data and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors drafted, revised and approved the final manuscript. Ian C.K. Wong and Frank M.C. Besag supervised the study. Ian C.K. Wong is the guarantor.

Competing interest statement: Ian C.K. Wong is a member of the NICE Epilepsy Guideline Group, and has received funding from various pharmaceutical companies, including GlaxoSmithKline, Janssen-Cilag, Pfizer and Therakind (manufacturers of lamotrigine, topiramate, gabapentin and midazolam, respectively); however, none of the funding is related to this study. Frank M.C. Besag has received lecture fees, consultancy fees, research grants and equipment grants from and has been sponsored to conferences by various pharmaceutical companies. He was previously Editor-in-Chief of a journal sponsored by GlaxoSmithKline. None of these monies have been paid directly to him; all monies since 2001 paid to NHS Trust. No monies are currently being received from pharmaceutical companies, nor from any source other than his employer, the NHS in the UK. Frank M.C. Besag has recently been sponsored to attend international epilepsy conferences by Eisai, the company that markets rufinamide in the UK. In addition, he is shortly to receive an unrestricted educational grant from Janssen-Cilag to hold a non-profit educational conference at the Royal College of Physicians on the Use of Psychotropic Drugs in Child and Adolescent Psychiatry. Elaine Hughes has received payment for teaching at educational meetings supported by Eisai, UCB Pharma and Janssen-Cilag. Ruth Ackers, Waney Squier and Macey L. Murray have no competing interests.

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