Epilepsia, 52(6):1150–1159, 2011
doi: 10.1111/j.1528-1167.2010.02952.x

FULL-LENGTH ORIGINAL RESEARCH

Combined analysis of risk factors for SUDEP

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Summary

Purpose: To pool data from four published case–control studies of sudden unexpected death in epilepsy (SUDEP) with live controls, to increase the power to determine risk factors.

Methods: Case–control studies from the United States, Sweden, Scotland, and England were combined. SUDEP was defined as (1) a history of epilepsy (>1 epileptic seizure during a period of <5 years); (2) death occurring suddenly; (3) death unexpected (i.e., no life-threatening illness); and (4) death remained unexplained after all investigative efforts, including autopsy. Definite SUDEP required all criteria. Logistic regression analyses adjusted for study. Further analysis simultaneously adjusted for study, age at death, gender, and duration of epilepsy.

Key Findings: Of the risk factors that could be analyzed across some or all studies, those that were statistically significant were increased frequency of generalized tonic–clonic seizures (GTCS), use of polytherapy, duration of epilepsy, young age at onset, gender, symptomatic etiology, and lamotrigine therapy. Results persisted when epilepsy onset was younger than 16 years and when it was 16 years or older. In univariate analysis, lamotrigine therapy was associated with significantly increased risk for SUDEP among individuals with idiopathic generalized epilepsy.

Significance: This analysis refines the identification of people with epilepsy that are at particular risk of SUDEP. The emerging profile indicates that people with early onset refractory symptomatic epilepsy with frequent GTCS and antiepileptic drug (AED) polytherapy are at higher risk. The results suggest that reduction of the number of GTCS is a priority, of more importance than reducing the number of AEDs. The role of AEDs and other treatment should be analyzed further in future studies.

KEY WORDS: SUDEP, Epilepsy, Case–control study.

Sudden unexpected death in epilepsy (SUDEP) is the most common condition-related cause of death in chronic epilepsy (Tomson et al., 2008; Surges et al., 2009). SUDEP is generally defined as the sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death in patients with epilepsy with or without evidence for a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a structural or toxicologic cause for death (Nashef, 1997). Cases fulfilling the above definition fall into the ''definite SUDEP'' category; sudden deaths occurring in benign circumstances with no known competing cause for death but without autopsy are classified as ''probable SUDEP.'' Cases where SUDEP cannot be excluded, either because of limited information regarding death circumstances or because there is a plausible competing explanation for death, are classified as ''possible SUDEP'' (Annegers, 1997).

Sudden death is at least 20 times more common in people with epilepsy compared with the general population (Ficker et al., 1998). The risk of SUDEP, however, varies widely within the epilepsy population (Tomson et al., 2008). There is a 100-fold range in SUDEP incidence within the epilepsy population, from 0.09 per 1,000 in prospective community-based studies of newly diagnosed patients up to 9 per 1,000 in epilepsy surgery candidates (Téllez-Zenteno et al., 2005; Tomson et al., 2008).

Case–control studies using living people with epilepsy as controls have aimed at identifying factors that distinguish the epilepsy patient at risk for SUDEP (Nilsson et al., 1999; Walczak et al., 2001; Langan et al., 2005; Hitiris et al., 2007). Patient demographics, seizure and epilepsy characteristics, comorbidities, and treatment with AEDs have thus to a variable extent been analyzed as risk factors in these

Accepted November 18, 2010; Early View publication January 28, 2011.

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studies. Some risk factors, for example, high frequency of generalized tonic–clonic seizures (GTCS), have been consistently identified. Results are inconsistent across studies and there is a lack of precision in the risk estimates, which, at least partly, can be attributed to small number of cases in most studies.

To counteract these limitations, the Task Force on Epidemiology explored the possibilities of pooling data from the major case–control studies of SUDEP. The present study is the result of this work.

Methods

We combined the data from the four case–control studies of risk factors for SUDEP, which used living people with epilepsy as controls; a U.S. study (Walczak et al., 2001), a Swedish study (Nilsson et al., 1999), a Scottish study (Hitiris et al., 2007), and an English study (Langan et al., 2005). In each study, SUDEP was defined as (1) a history of epilepsy (more than one epileptic seizure during a period of <5 years); (2) death occurring suddenly; (3) death unexpected (i.e., there was no life-threatening illness); and (4) death remaining unexplained after all investigative efforts, including autopsy. Definite SUDEP required all four criteria and probable required criteria 1–3. The methods of each of these studies are described briefly below.

Description of cohorts

U.S. study

Definite and probable cases of SUDEP were identified from three upper Midwestern epilepsy centers between June 1, 1991 and December 31, 1996. For each case of SUDEP, four controls were randomly selected from people enrolled during the same month at the same epilepsy center. Potential SUDEP risk factors were ascertained through chart review. The total study consisted of 20 cases and 80 controls (Walczak et al., 2001).

Swedish study

Cases and controls were drawn from Stockholm residents aged 15–70 years, who were discharged from hospital with a diagnosis of epilepsy between 1980 and 1989. Definite and probable SUDEP cases were drawn from this cohort if they had died by December 31, 1991 and had a diagnosis of epilepsy on the death certificate, and did not die due to status epilepticus or accidents. For each case of SUDEP, three living controls were randomly drawn from the study population and matched on year of birth, sex, and assessment period. Cases and controls were restricted to those who received at least one continuous year of valproate, phenytoin, or carbamazepine therapy. Medical records were abstracted to obtain information on risk factors for cases and controls and then reviewed by the same two neurologists. The total study consisted of 56 cases and 157 controls (Nilsson et al., 1999).

Scottish study

Cases with definite or probable SUDEP were drawn from people with active seizure disorders, registered with the Epilepsy Unit since 1982. For each case, two living controls were randomly selected from the Epilepsy Unit population and matched on year of birth, gender, and syndrome classification (i.e., idiopathic, cryptogenic, or symptomatic). Clinical data on possible risk factors for SUDEP were abstracted from the medical record according to a structured protocol. The total study consisted of 64 cases and 119 controls (Hitiris et al., 2007).

English study

Between 1989 and 1998, cases, aged 16–50 years, with SUDEP were identified by coroners, neurologists, self-referred by family members, and by the charity Epilepsy Bereaved. Four controls with epilepsy were randomly selected from a diagnostic index and a prescription database and matched to each SUDEP case according to age and geographic location. Potential SUDEP risk factors were ascertained from medical records for controls and from semistructured interviews with family members, general practitioners, and hospital consultants for cases. The total study consisted of 149 cases and 602 controls (Langan et al., 2005).

Combined cohort

The combined cohort consisted of cases and controls from the four studies, excluding six cases with evidence of a history of heart disease that did not account for sudden death on the autopsy. An additional 28 controls were excluded because they had a history of heart disease. Therefore, the final sample consisted of 289 cases and 958 controls (Table S1).

Potential SUDEP risk factors

Information on risk factors was not collected in the same way for all factors across all studies. Whenever the same factor was collected across more than one study, it was defined for the combined analysis according to the categorization that could be applied to all datasets with that specific piece of information. We considered several risk factors for SUDEP, including demographic characteristics, seizure characteristics, antiepileptic drugs (AEDs), and comorbidities.

Risk factors included in all four studies

We considered gender, age at onset of epilepsy, duration of epilepsy, and age (defined as age at death for cases and age at the cases' death for controls). Idiopathic/cryptogenic etiology was defined according to the epidemiologic definition (Commission, 1993) and refers to epilepsy of unknown

cause. Dummy variables were formed to evaluate monotherapy with any AED and polytherapy compared to no AED therapy.

Risk factors in three of the four studies

England, Scotland, and Sweden: We evaluated the association between idiopathic generalized epilepsy (IGE) and SUDEP and the interaction between gender and IGE.

England, United States, and Sweden: We considered the impact of a history of epilepsy surgery on the risk for SUDEP as well as the yearly frequency of GTCS (as none, 1–2, ≥3, and unknown), and the combined effect of yearly frequency of GTCS (as none, 1–2 or unknown frequency, and ≥3) and no therapy or monotherapy versus polytherapy. In the analysis, the group with unknown GTCS frequency was combined with the group with 1–2 GTCS because results were similar for these groups. Finally, we examined the association between SUDEP and a comorbid mental health disorder.

England, United States, and Scotland: We examined the association between lamotrigine therapy and SUDEP.

United States, Scotland, and Sweden: We considered antemortem AED levels in the U.S., Scottish, and Swedish studies. High levels were defined as >12 mg/L for carbamazepine, 20 mg/L for phenytoin, and 100 mg/L for valproic acid. Low levels were defined as <3 mg/L for carbamazepine, 10 mg/L for phenytoin, and 40 mg/L for valproic acid.

Risk factors in two of the four studies

England and United States: We assessed the relationship between mental retardation (defined as a full scale IQ < 70 or as ''mental retardation'') and SUDEP.

England and Sweden: In these studies, it was possible to evaluate the relationship between SUDEP and the presence of comorbid alcohol abuse and lung disorders.

England and Scotland: Within these studies, we assessed the interaction between lamotrigine therapy and IGE on the risk for SUDEP.

Statistical analysis

Data were analyzed with SAS (SAS Institute, Cary, NC, U.S.A.), using the Mantel-Haenszel method for categorical variables with testing at the two-tailed level of 0.05.

The original studies were matched on one or more factors. For the combined analysis, we ignored the matching, but adjusted for study, age (a matching variable in three of the four studies), and gender (a matching variable in two of the four studies). Clinic was a matching variable in the U.S. study and general practice region was a matching variable in the study from England. After a subgroup analysis restricted to the U.S. study, we did not observe a significant difference in the results before and after additional adjustment for clinic. Therefore, this factor is not adjusted for in our analyses.

Risk factors for SUDEP were examined using logistic regression. Crude analyses were adjusted for study with the English study as the referent and the U.S. study as the referent when the English study was excluded from the analysis. Multivariate analysis adjusted for study, age, gender, and duration of epilepsy. Because age at epilepsy onset <16 years was associated with SUDEP risk (Nilsson et al., 1999), we conducted separate crude analyses of SUDEP risk factors stratifying by age at epilepsy onset >16 years and ≤16 years in order to determine whether SUDEP risk factors were different in children compared to adults. To test whether the use of logistic regression was suitable for this study, we compared the results obtained from a standard logistic regression analysis with results from an analysis in which we used nonlinear mixed methods, assuming a binomial distribution for the dependent variable, with a random intercept for each data source (Friedenreich, 1993). Because both analyses yielded similar results, we concluded that logistic regression was a suitable approach.

Results

Across the four studies, after exclusions (cases = 6; controls = 28) there were 289 cases and 958 controls (Table 1). Compared to controls, cases were more likely to have longer duration of epilepsy ($p < 0.001$), less likely to have idiopathic/cryptogenic etiology ($p = 0.026$), and more likely to be on polytherapy ($p < 0.001$). Greater frequency of GTCS was observed in cases from England, the United States, and Sweden ($p = 0.001$). Cases were more likely than controls to be taking lamotrigine ($p = 0.002$) in grouped data from England, the United States, and Scotland.

Demographic variables

Several predictors of SUDEP were identified. Male gender was associated with a 1.4-fold increased risk for SUDEP. Compared to people with an onset age between 16 and 60 years, patients with onset of epilepsy younger than 16 years had a statistically significant 1.72-fold increased risk for SUDEP; those with onset after age 60 were 60% less likely to have SUDEP, but this was not statistically significant (Table 1).

Epilepsy factors

Duration of epilepsy for more than 15 years was associated with a 1.95-fold increased risk of SUDEP. Increasing number of GTCS per year was associated with a statistically significant increased risk for SUDEP compared with people without GTCS [odds ratio (OR) 2.94 for 1–2 GTCS, OR 8.28 for 3–12 GTCS, OR 9.06 for 13–50 GTCS, and OR 14.51 for >50 GTCS]. Polytherapy was also associated with increased risk. When frequency of GTCS and antiepileptic drug (AED) therapy were considered together, we found a gradient in risk for SUDEP. Compared to those without GTCS on no AED therapy or monotherapy, the risk

Table 1. Risk factors for SUDEP in combined analysis

Variable	Cases Frequency (%)	Controls Frequency (%)	Crude[a] OR	Crude[a] 95% CI	Adjusted[b] OR	Adjusted[b] 95% CI
All data sources[c]						
Gender						
Female	118 (40.8)	453 (47.3)	1.00 (Ref)	–	1.00 (Ref)	–
Male	171 (59.2)	505 (52.7)	1.30	0.99–1.69	1.42	1.07–1.88
Onset age[d]						
<16 years	166 (59.5)	480 (52.0)	1.85	1.36–2.52	1.72	1.23–2.40
Between 16 and 60 years	111 (39.8)	430 (46.6)	1.00 (Ref)	–	1.00 (Ref)	–
>60 years	2 (0.7)	13 (1.4)	0.48	0.11–2.19	0.41	0.08–2.14
Duration of epilepsy[e]						
≤15 years	115 (41.1)	500 (53.5)	1.00 (Ref)	–	1.00 (Ref)	–
>15 years	165 (58.9)	434 (46.5)	1.84	1.39–2.43	1.95	1.45–2.63
Age at death[f]						
<25 years	49 (17.0)	195 (20.4)	1.00 (Ref)	–	1.00 (Ref)	–
Between 25 and 34 years	107 (37.2)	358 (37.5)	1.19	0.81–1.75	0.95	0.63–1.43
Between 35 and 44 years	79 (27.4)	243 (25.5)	1.22	0.81–1.83	0.82	0.53–1.29
Between 45 and 55 years	36 (12.5)	112 (11.7)	1.10	0.67–1.82	0.72	0.42–1.23
>55 years	17 (5.9)	46 (4.8)	1.14	0.58–2.25	0.89	0.44–1.79
Idiopathic etiology[g]						
No	135 (50.4)	433 (45.7)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	133 (49.6)	514 (54.3)	0.68	0.49–0.96	0.71	0.50–1.01
Comparisons with polytherapy[h]						
No AED therapy	18 (6.4)	88 (9.3)	1.00 (Ref)	–	1.00 (Ref)	–
Monotherapy	102 (36.4)	540 (56.8)	0.89	0.51–1.55	0.74	0.42–1.31
Polytherapy	160 (57.1)	322 (33.9)	2.50	1.43–4.38	1.95	1.09–3.47
England, Scotland, and Sweden[c]						
Idiopathic generalized epilepsy[i]						
No	165 (66.5)	456 (52.6)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	83 (33.5)	411 (47.4)	0.72	0.51–1.01	0.69	0.49–0.98
Gender and Idiopathic generalized epilepsy[i]						
Females without idiopathic generalized epilepsy	74 (29.8)	200 (23.1)	1.00 (Ref)	–	1.00 (Ref)	–
Females with idiopathic generalized epilepsy	26 (10.5)	214 (24.7)	0.43	0.26–0.72	0.39	0.23–0.67
Males without idiopathic generalized epilepsy	91 (36.7)	256 (29.5)	0.98	0.68–1.40	1.03	0.70–1.50
Males with idiopathic generalized epilepsy	57 (23.0)	197 (22.7)	1.00	0.65–1.54	1.04	0.67–1.62
England, the United States, and Sweden[c]						
Had surgery[j]						
No	215 (96.8)	807 (96.8)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	7 (3.2)	27 (3.2)	1.01	0.41–2.51	0.91	0.36–2.30
GTCS frequency per year						
0	38 (16.9)	539 (64.2)	1.00 (Ref)	–	1.00 (Ref)	–
1–2	33 (14.7)	94 (11.2)	5.10	3.01–8.64	5.07	2.94–8.76
≥3	108 (48.0)	100 (11.9)	15.56	10.10–23.97	15.46	9.92–24.10
Unknown	46 (20.4)	106 (12.6)	6.12	3.78–9.89	5.35	3.21–8.91
GTCS frequency per year and AED therapy						
No GTCS and (no therapy or monotherapy)	21 (9.7)	386 (46.6)	1.00 (Ref)	–	1.00 (Ref)	–
No GTCS and polytherapy	16 (7.4)	145 (17.4)	2.20	0.54–1.22	1.87	0.93–3.75
(1–2 or unknown GTCS) and (no therapy or monotherapy)	32 (14.8)	123 (14.8)	4.92	2.37–8.87	4.46	2.43–8.19
(1–2 or unknown GTCS) and polytherapy	40 (18.5)	77 (9.3)	10.40	5.69–19.02	9.18	4.96–16.97
≥3 GTCS and (no therapy or monotherapy)	26 (12.0)	36 (4.3)	13.90	7.09–27.26	13.49	6.78–26.83
≥3 GTCS and polytherapy	81 (37.5)	64 (7.7)	25.20	14.36–44.24	22.64	12.77–40.14
Comorbid mental health disorder[j]						
No	208 (95.0)	779 (93.3)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	11 (5.0)	56 (6.7)	0.67	0.34–1.31	0.63	0.31–1.28

Continued

Table 1. Continued

Variable	Cases Frequency (%)	Controls Frequency (%)	Crude[a] OR	Crude[a] 95% CI	Adjusted[b] OR	Adjusted[b] 95% CI
England, the United States, and Scotland[c]						
Lamotrigine therapy[m]						
No	181 (80.8)	712 (89.8)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	43 (19.2)	81 (10.2)	1.91	1.26–2.88	1.86	1.22–2.84
The United States, Scotland, and Sweden[n]						
CBZ level >12 mg/L						
No	135 (96.4)	349 (98.0)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	5 (3.6)	7 (2.0)	1.69	0.52–5.48	1.15	0.34–3.86
CBZ level <3 mg/L						
No	52 (37.1)	107 (30.1)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	88 (62.9)	249 (69.9)	0.72	0.47–1.09	0.81	0.52–1.24
PHT level >20 mg/L						
No	132 (94.3)	336 (94.4)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	8 (5.7)	20 (5.6)	1.13	0.48–2.67	0.96	0.39–2.38
PHT level <10 mg/L						
No	33 (23.6)	75 (21.1)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	107 (76.4)	281 (78.9)	0.74	0.45–1.23	0.89	0.53–1.50
VPA level >100 mg/L						
No	137 (97.9)	351 (98.6)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	3 (2.1)	5 (1.4)	2.04	0.45–9.16	2.77	0.54–14.13
VPA level <40 mg/L						
No	20 (14.3)	49 (13.8)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	120 (85.7)	307 (86.2)	1.05	0.58–1.90	1.08	0.59–2.01
England and the United States[c]						
Learning difficulty[o]						
No	112 (71.3)	500 (78.4)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	45 (28.7)	138 (21.6)	1.46	0.98–2.16	1.38	0.91–2.09
England and Sweden[c]						
Alcohol abuse[b]						
No	167 (82.3)	635 (88.2)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	36 (17.7)	85 (11.8)	1.49	0.96–2.33	1.63	0.99–2.66
Comorbid pulmonary disease[q]						
No	189 (94.0)	667 (91.0)	1.00 (Ref)	–	1.00 (Ref)	–
Yes	12 (6.0)	66 (9.0)	0.67	0.35–1.26	0.77	0.40–1.48
England and Scotland[c]						
Lamotrigine therapy and idiopathic generalized epilepsy[r]						
No lamotrigine therapy without idiopathic generalized epilepsy	98 (52.1)	269 (37.9)	1.00 (Ref)	–	1.00 (Ref)	–
No lamotrigine therapy with idiopathic generalized epilepsy	54 (28.7)	372 (52.4)	0.50	0.34–0.74	0.50	0.33–0.74
Lamotrigine therapy without idiopathic generalized epilepsy	18 (9.6)	42 (5.9)	1.04	0.57–1.92	1.02	0.55–1.90
Lamotrigine therapy with idiopathic generalized epilepsy	18 (9.6)	27 (3.8)	2.20	1.14–4.23	1.85	0.94–3.64

[a]Adjusted for data source.
[b]Adjusted for data source, gender, age at death, and duration of epilepsy.
[c]Referent data source = England.
[d]Missing information for 10 (3.5%) cases and 35 (3.7%) controls.
[e]Missing information for 9 (3.1%) cases and 24 (2.5%) controls.
[f]Missing information for 1 (0.4%) case and 4 (0.4%) controls.
[g]Missing information for 21 (7.3%) cases and 11 (1.2%) controls.
[h]Missing information for 16 (5.5%) cases and 35 (3.7%) controls.
[i]Missing information for 21 (7.8%) cases and 11 (1.3%) controls.
[j]Missing information for 3 (1.3%) cases and 5 (0.6%) controls.
[k]Missing information for 9 (4.0%) cases and 8 (1.0%) controls.
[l]Missing information for 6 (2.7%) cases and 4 (1.0%) controls.
[m]Missing information for 9 (3.9%) cases and 8 (0.3%) controls.
[n]Referent data source = United States.
[o]Missing information for 12 (7.1%) cases and 44 (6.5%) controls.
[p]Missing information for 2 (1.0%) cases and 39 (5.1%) controls.
[q]Missing information for 4 (2.0%) cases and 26 (3.4%) controls.
[r]Missing information for 25 (11.7%) cases and 11 (1.5%) controls.

for SUDEP was statistically significantly increased, 4.92-fold for those with 1–2 GTCS or unknown number on no therapy or monotherapy, 10.40-fold for those with 1–2 GTCS or unknown GTCS and polytherapy, 13.90-fold for those with ≥3 GTC and no therapy or monotherapy, and 25.20-fold for those with ≥3 GTCS and polytherapy. These results suggest that GTCS frequency and polytherapy contributed to SUDEP risk (Table 1).

Idiopathic/cryptogenic etiology and idiopathic generalized epilepsy (IGE) were associated with a lower risk for SUDEP. We considered whether there was an interaction between IGE and gender on the risk for SUDEP. Compared with female patients without IGE, female patients with IGE were protected from developing SUDEP (OR 0.39), but a similar relationship was not observed for male patients with or without IGE.

Antiepileptic drug therapy

Compared to no AED therapy, polytherapy was associated with a statistically significant increased risk for SUDEP. Monotherapy was protective for SUDEP, but this was not statistically significant (Table 1).

We examined high antemortem blood levels of carbamazepine, phenytoin, and valproic acid as possible SUDEP risk factors; only valproic acid levels >100 mg/L were associated with an increased SUDEP risk, but this was not statistically significant. Low blood levels of each of the three monotherapies were not associated with SUDEP.

Comorbidities

There was a suggestion of associations between a history of alcohol abuse, learning difficulty, and SUDEP, although these associations did not reach statistical significance. Other comorbidities, including mental health disorders and lung disease, were not significantly associated with SUDEP (Table 1).

Analysis stratified by age at epilepsy onset

We examined whether risk factors for SUDEP differed by age at epilepsy onset stratified as <16 years and ≥16 years (Table 2). Among those with a younger age at epilepsy onset, a longer duration of epilepsy was associated with a 3.2-fold increased risk of SUDEP, as was >2 GTCS per year. Among those with an older age at onset, the risk for SUDEP was increased among male patients, among those with alcohol abuse, whereas a longer duration of epilepsy and idiopathic etiology were protective. In addition, in the older age group, the risk for SUDEP was increased among those with alcohol abuse. However, after additional adjustment for number of GTCS and for age at death, the association between alcohol abuse and SUDEP was no longer significant [OR 1.86; 95% confidence interval (CI) 0.98–3.53]. AED monotherapy was associated with a significant protective effect for SUDEP for those with older age at onset only, whereas polytherapy was associated with an increased risk for developing SUDEP for those with a younger age at onset only (Table 2). There was a statistically significant increased risk for developing SUDEP among those on lamotrigine therapy in the younger age at onset group.

Discussion

We found that increased frequency of GTCS, use of polytherapy, duration of epilepsy, young age at onset, gender, symptomatic etiology, and lamotrigine therapy were significantly associated with SUDEP (Table 3). It is important to understand that this does not mean that people with idiopathic epilepsy or those with a few GTCS per year are protected from SUDEP. In fact, such patients represented a significant proportion of the cases in the included studies (Table 1). The observed relationships persisted in analysis restricted to epilepsy onset at age younger than 16 years and to onset at age 16 years or older. In addition, lamotrigine therapy was associated with significantly increased risk for SUDEP when prescribed to individuals with IGE in univariate analyses restricted to pooled data from England and Scotland (Table 1). These observations are in line with those of previous uncontrolled case-series observations suggestive of an association between SUDEP risk and lamotrigine treatment of idiopathic epilepsy (Aurlien et al., 2007). Various mechanisms have been proposed for this potential association (Nashef & Ryvlin, 2009). These include the possibility of less efficacy of lamotrigine in some specific idiopathic epilepsy syndromes. Arrhythmogenic cardiac effects, perhaps through lamotrigine inhibition of the delayed rectifier potassium ion current (Ikr), have been proposed as another mechanism (Danielsson et al., 2005). Among women, those with IGE were at a lower risk for SUDEP compared to those without IGE in pooled data from England, Scotland, and Sweden. Compared to people with no GTCS on no AED therapy or monotherapy, 1–2 GTCS per year was associated with increased risk for SUDEP among those on monotherapy and those on polytherapy as was >3 GTCS per year in pooled data from England, the United States, and Sweden. Comorbid mental health disorders were protective for SUDEP in the pooled data from England, United States, and Sweden. This association, although not statistically significant, could theoretically be a reflection of medication for the comorbidity, since it has been suggested that treatment with SSRI antidepressants, that raise serotonin levels, might reduce the SUDEP risk (Tupal & Faingold, 2006). Interestingly, monotherapy was associated with a lower risk for SUDEP in those with epilepsy onset at 16 years or older, but not for those with onset younger than 16. In contrast, the increased risk for SUDEP associated with polytherapy was limited to those with younger age at onset. We have no obvious explanation for this discrepancy by age at onset. Other age-dependent circumstances might contribute. Nighttime supervision was shown to be protective in the United Kingdom study (Langan et al.,

Table 2. Risk factors for SUDEP in combined analysis by age of epilepsy onset

	Onset age <16 years[a]		Onset age ≥16 years[a]	
Variable	OR[b]	95% CI	OR[b]	95% CI
All data sources[b]				
Gender				
Female	1.00 (Ref)	–	1.00 (Ref)	–
Male	1.25	0.86–1.82	1.88	1.20–2.94
Duration of epilepsy				
≤15 years	1.00 (Ref)	–	1.00 (Ref)	–
>15 years	3.20	2.07–4.97	0.59	0.37–0.94
Age at death				
<25 years	1.00 (Ref)	–	1.00 (Ref)	–
Between 25 and 34 years	1.26	0.79–2.03	1.56	0.68–3.61
Between 35 and 44 years	1.28	0.74–2.21	1.76	0.76–4.08
Between 45 and 55 years	1.62	0.82–3.21	1.36	0.53–3.48
>55 years	2.14	0.32–14.43	2.19	0.79–6.11
Idiopathic etiology				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	0.75	0.49–1.15	0.53	0.29–0.96
Comparisons with no AEDs				
No AED therapy	1.00 (Ref)	–	1.00 (Ref)	–
Monotherapy	2.14	0.64–7.23	0.48	0.24–0.95
Polytherapy	7.90	2.37–26.37	0.87	0.42–1.78
England, Scotland, and Sweden[b]				
Idiopathic generalized epilepsy				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	0.63	0.41–0.96	0.49	0.26–0.92
Gender and idiopathic generalized epilepsy				
Females without idiopathic generalized epilepsy	1.00 (Ref)	–	1.00 (Ref)	–
Females with idiopathic generalized epilepsy	0.43	0.23–0.80	0.16	0.04–0.57
Males without idiopathic generalized epilepsy	0.99	0.56–1.75	1.26	0.75–2.12
Males with idiopathic generalized epilepsy	0.85	0.49–1.47	0.98	0.46–2.09
England, the United States, and Sweden[c]				
Had surgery				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	1.26	0.44–3.64	0.55	0.07–4.63
GTCS frequency per year				
0	1.00 (Ref)	–	1.00 (Ref)	–
1–2	6.60	3.25–13.40	3.46	1.51–7.95
≥3	18.92	10.72–33.41	10.18	5.08–20.40
Unknown	3.91	1.93–7.95	5.73	2.75–11.94
GTCS frequency per year and AED therapy				
No GTCS and (no therapy or monotherapy)	1.00 (Ref)	–	1.00 (Ref)	–
No GTCS and polytherapy	3.12	1.29–7.52	1.16	0.37–3.63
(1–2 or unknown GTCS) and (no therapy or monotherapy)	5.60	2.44–12.86	3.07	1.28–7.35
(1–2 or unknown GTCS) and polytherapy	9.51	4.07–22.23	8.20	3.40–19.78
≥3 GTCS and (no therapy or monotherapy)	12.19	4.64–32.00	12.57	4.81–32.84
≥3 GTCS and polytherapy	37.45	17.66–79.42	9.77	4.00–23.88
Comorbid mental health disorder				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	0.62	0.24–1.57	0.55	0.19–1.64
England, the United States, and Scotland[c]				
Lamotrigine therapy				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	2.32	1.33–4.03	1.72	0.88–3.38
The United States, Scotland, and Sweden[d]				
CBZ level >12 mg/L				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	1.86	0.37–9.38	0.87	0.09–8.07
PHT level >20 mg/L				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	1.48	0.38–5.73	0.90	0.25–3.27
VPA level >100 mg/L				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	2.79	0.47–16.38	–	–

Continued

Table 2. Continued

Variable	Onset age <16 years[a]		Onset age ≥16 years[a]	
	OR[b]	95% CI	OR[b]	95% CI
CBZ level <3 mg/L				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	0.99	0.51–1.93	0.77	0.42–1.39
PHT level <10 mg/L				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	0.91	0.41–2.02	0.70	0.35–1.39
VPA level <40 mg/L				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	0.73	0.31–1.70	3.22	0.92–11.29
England and the United States[c]				
Learning difficulty				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	2.44	1.52–3.90	0.40	0.17–0.94
England and Sweden[c]				
Alcohol abuse				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	0.89	0.37–2.12	2.71	1.50–4.88
Comorbid pulmonary disease				
No	1.00 (Ref)	–	1.00 (Ref)	–
Yes	0.65	0.29–1.44	0.69	0.23–2.07
England and Scotland[c]				
Lamotrigine therapy and idiopathic generalized epilepsy				
No lamotrigine therapy without idiopathic generalized epilepsy	1.00 (Ref)	–	1.00 (Ref)	–
No lamotrigine therapy with idiopathic generalized epilepsy	0.38	0.23–0.62	0.55	0.28–1.09
Lamotrigine therapy without idiopathic generalized epilepsy	0.84	0.31–2.32	1.63	0.73–3.65
Lamotrigine therapy with idiopathic generalized epilepsy	2.08	0.94–4.60	0.86	0.17–4.34

[a]Missing information on age at onset for 45 patients [35 (3.7%) controls and 10 (3.5%) cases].
[b]Adjusted for data source.
[c]Referent data source = England.
[d]Referent data source = the United States.

2005). Such supervision is likely to be more common among younger people living with their parents and could perhaps modify the risks of untreated epilepsy.

Results of pooled data from all four case–control studies are consistent with some results from the individual studies. The analysis also revealed several risk factors that were not previously identified in any of the studies by themselves, including lamotrigine therapy, male gender, and symptomatic etiology. We were unable to confirm associations between SUDEP and seizure frequency in general (Nilsson et al., 1999; Walczak et al., 2001), although we found a relationship between frequency of GTCS and SUDEP. Data for some factors were collected only in individual studies, including full scale IQ (Walczak et al., 2001), dementia (Nilsson et al., 1999), absence of cardiovascular disease (Nilsson et al., 1999), number of dose changes per year (Nilsson et al., 1999), anxiolytics (Nilsson et al., 1999), seizures in the last year before SUDEP (Hitiris et al., 2007), not treated with AEDs (Langan et al., 2005), and sleeping alone in a room (Langan et al., 2005).

In any combined analysis, the methodologic concern is that heterogeneity in the populations and methods may influence the pooled results. A significant strength of our pooled analysis is that case and control definitions and risk factor ascertainment were consistent across the four studies, lessening the chance that heterogeneity influenced the results. In all four studies, cases were definite or probable SUDEP, and controls were people with epilepsy who were alive and were selected from the same population that gave rise to the cases. Risk factors in each study were ascertained through chart review. A potential weakness is that there are differences between the studies in the ratio of matching cases to controls, the matching variables, and whether age was restricted. The Swedish study was confined to cases and controls who received at least 1 year of valproate, phenytoin, or carbamazepine therapy. Not all the risk factors examined in the combined analysis were collected in all four studies. Because of these differences between studies, we evaluated whether meaningful heterogeneity existed. First we adjusted for study, age at death, gender, and duration of epilepsy, which were matching variables used in at least one study and assessed in all four studies. Second, we compared results from the logistic regression analysis to those obtained with nonlinear mixed models with a random intercept for each study (Friedenreich, 1993). Results of these analyses were essentially the same, supporting a lack of meaningful heterogeneity. A second potential weakness is that the English study was at least threefold larger than any of the other studies and could overly influence the combined results. Instead we found that only one of the six significant

Table 3. Statistically significant risk factors[a] for SUDEP across studies and in the combined analysis

England	United States	Sweden	Scotland	Combined
History of GTCS	↑Frequency of GTCS[b]	Polytherapy	Age at onset	↑Frequency of GTCS
↑Frequency of GTCS	Polytherapy	↑Seizure frequency[c,d]	Seizure in last year	Polytherapy[f]
Lifetime number of AEDs	↑Seizure frequency[b]	Number of AEDs[d]		↑Duration of epilepsy[f]
No AED treatment ever	↑Duration of epilepsy	Dementia		Age at onset
Current use of carbamazepine	Full scale IQ <70	No CVD		Gender[f]
Sleeping alone in room	Number of AEDs at last visit	Age at onset[c]		Symptomatic etiology
No asthma		Number of dose changes per year[e]		Lamotrigine therapy[g]
		Anxiolytics[c]		Idiopathic generalized epilepsy[g,h]
		Other injuries		↑Seizure frequency & ↑number of AEDs[g]
		↑Seizure frequency & ↑number of AEDs		Learning disability[j]
				Alcohol abuse[j]
				No Lamotrigine therapy & no IGE
				Lamotrigine therapy & IGE

[a]Statistically significant risk factors in each of the individual studies are listed whether or not they could be analyzed in the combined analysis.
[b]Finding overall and restricted to women in subanalysis.
[c]Finding overall and restricted to men in subanalysis.
[d]Findings in multivariate model that included seizure frequency in the past year, age at epilepsy onset, epilepsy type, number of AEDs, changes in AED dose per year.
[e]Finding overall and restricted to women in subanalysis.
[f]Findings overall and restricted to age of onset <16 years.
[g]Findings overall and restricted to age of onset <16 years and age of onset ≥16 years.
[h]Finding among females and restricted to females with age of onset <16 years and age of onset ≥16 years.
[i]Finding only in analysis restricted to age of onset <16 years and age of onset ≥16 years.
[j]Finding only those with age of onset ≥16 years.

risk factors from the English study persisted in the pooled analysis.

This combined analysis helps refine the identification of people with epilepsy at a particular increased risk of SUDEP. The emerging profile is the person with early onset refractory symptomatic epilepsy with frequent GTCS and AED polytherapy. The data suggest that the priority should be to minimize the number of GTCS, which is more important than reducing the number of AEDs. The roles of AEDs and other pharmacologic treatment should be analyzed further in future studies. This is particularly important considering the suggestion of lamotrigine as a potential SUDEP risk factor, which will need to be confirmed or refuted in independent studies. A further challenge for future research is to focus on patients with refractory epilepsy to clarify what features may distinguish the patients in this high-risk population who die in SUDEP from those who survive.

Acknowledgments

The authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

Ettore Beghi: Pharmaceutical companies supporting studies are GlaxoSmithKline, EISAI, Sanofi-Aventis, and Sigma-Tau. Emma Benn: None. Martin Brodie: Scientific Advisory Boards of Pfizer, UCB Pharma, Eisai, GSK, Novartis, Valeant, Sierra Neuropharmaceuticals, and Medtronic; and speaker's honoraria from UCB, Eisai, GSK, Novartis, and Valeant. W. Allen Hauser: Consultant for Pfizer and GlaxoSmithKline. Dale Hesdorffer: Advisory board for Pfizer. Yvonne Langam: None. Lena Nilsson: None. Josemir W Sander: Honoraria, consultancy fees, research grants from various pharmaceutical companies including UCB, Eisai, Janssen-Cilag, and GlaxoSmithKline. Torbjorn Tomson: Research grants and/or speakers honoraria from: Eisai, GlaxoSmithKline, Janssen-Cilag Novartis, Sanofi-Aventis, Pfizer, and UCB-Pharma. Thaddeus S. Walczak: None.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary characteristics by data source.

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