

Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials



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Summary

Background Sudden unexpected death in epilepsy (SUDEP) represents the main cause of death in patients with refractory epilepsy. No evidence-based intervention to prevent SUDEP exists. We postulated that pooling data from randomised placebo-controlled trials in patients with refractory epilepsy might show a lower incidence of SUDEP in patients receiving antiepileptic drugs (AEDs) at efficacious doses than in those receiving placebo.

Methods We searched Medline and the Cochrane Library for randomised trials investigating any AED in the add-on treatment of drug-resistant epilepsy in adults. We extracted the number and causes of death in patients allocated to AEDs at doses that were more efficacious than placebo against seizures, AEDs at non-efficacious doses, and placebo. In our primary analysis, we compared the occurrence of definite or probable SUDEP between patients given efficacious AED doses and those given placebo using the Mantel-Haenszel method, with exclusion of trials with no event.

Findings Data of 33 deaths, including 20 deemed as SUDEP, were extracted from 112 eligible randomised trials. 18 deaths were classified as definite or probable SUDEP and two as possible SUDEP. Definite or probable SUDEP, all SUDEP, and all causes of death were significantly less frequent in the efficacious AED group than in the placebo group, with odds ratios of 0.17 (95% CI 0.05–0.57, $p=0.0046$), 0.17 (0.05–0.57, $p=0.0046$), and 0.37 (0.17–0.81, $p=0.0131$), respectively. Rates of definite or probable SUDEP per 1000 person-years were 0.9 (95% CI 0.2–2.7) in patients who received efficacious AED doses and 6.9 (3.8–11.6) in those allocated to placebo.

Interpretation Treatment with adjunctive AEDs at efficacious doses may have reduced the incidence of definite or probable SUDEP by more than seven times compared with placebo in patients with previously uncontrolled seizures. This result provides evidence in favour of active treatment revision for patients with refractory epilepsy.

Funding None.

Introduction

Mortality is increased in patients with uncontrolled seizures,^{1,2} mainly owing to sudden unexpected death in epilepsy (SUDEP). Incidence of SUDEP is between 3.5 and 9.3 per 1000 person-years in refractory epilepsy,³ and at least 12% of patients with childhood epilepsy and no terminal 5-year remission will die of SUDEP by the age of 40 years.^{1,2} Indeed, most SUDEP victims are young adults with a mean age at the time of death of about 35 years.^{2,4,5} SUDEP is typically unwitnessed and occurs during sleep, but SUDEP that is observed is usually triggered by a seizure through mechanisms that remain uncertain.³ Some potentially preventable risk factors have been identified,^{3,4,6–9} suggesting that a significant proportion of SUDEP could be avoidable with optimal care.^{10,11} However, despite an urge to develop such a strategy, no intervention has yet been assessed in a controlled study.

Meta-analysis of randomised placebo-controlled trials done in patients with refractory epilepsy offers a unique opportunity to investigate this issue. These trials assess the potency of adjunctive antiepileptic drugs (AEDs) to reduce frequency of seizures, a risk factor for SUDEP.^{4,7,9} However, because polytherapy might also promote SUDEP,^{3,4,7–9} the net effect of adding another AED

cannot be predicted. Although SUDEP rarely occurs during such randomised trials, pooling of data across a large number of trials might allow to detect the effect of adjunctive AED treatment on the risk of SUDEP. More specifically, we hypothesised that the incidence of definite and probable SUDEP would be lower in patients receiving AEDs at efficacious doses than in those receiving placebo. Our secondary aims were to compare the rate of all SUDEP (possible, probable, or definite), deaths from causes other than SUDEP, and the total number of deaths between the two groups.

Methods

Search strategy and selection criteria

We selected double-blind, placebo-controlled randomised trials of add-on AEDs done in adult patients with uncontrolled partial or primary generalised tonic-clonic seizures. Two electronic databases (Medline and the Cochrane Library) were searched from Jan 1, 1960, to Dec 31, 2010. We looked for additional studies in the register of the ISRCTN, the metaRegister of Controlled Trials, ClinicalTrials.gov, Cochrane meta-analyses of AEDs, and references of all identified publications. The detailed search strategy is provided in the webappendix (pp 1–2).

Lancet Neurol 2011; 10: 961–68

Published Online
September 20, 2011
DOI:10.1016/S1474-4422(11)70193-4

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See Online for webappendix

Data extraction

We extracted the following information from the selected publications: description of treatment groups, baseline and treatment period duration, seizure type, number of withdrawals and deaths per group, and reasons for death. We considered only those deaths that occurred after the first dose intake and less than 7 days after the last dose intake. We asked the sponsors of relevant trials to provide a detailed narrative for every recorded death.

The cause of death was independently assessed by two of the authors (PR and SR), on the basis of all available data and present definitions of SUDEP.^{12,13} A consensual conclusion was then reached to classify every death as possible, probable, or definite SUDEP, or other causes of death. SUDEP was defined as a sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of patients with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, in whom post-mortem examination did not reveal a structural or toxicological cause of death.¹² The term “unexpected” refers to a death that occurs while in a reasonable state of health (apart from epilepsy), during normal activities and benign circumstances, and without any obvious medical cause.¹³ SUDEP was classified into three categories:¹³ definite SUDEP for the cases that fulfilled the above definition; probable SUDEP, for those in which post-mortem data were not available, but all other criteria were fulfilled; and possible SUDEP, for those in which criteria of probable SUDEP were not fulfilled, either because of missing information about the circumstances of death or because there was a plausible competing explanation for death.

Quality assessment

The Cochrane Collaboration’s method to assess risk of bias was used to ascertain the validity of eligible randomised trials.¹⁴ The risk of selective outcome reporting for the occurrence of death was classified into three categories: absent, when all serious adverse events that occurred during the trial were detailed in the publication, or when the occurrence or absence of deaths was explicitly specified in the publication or by the study sponsor; unclear, when the criteria for absence of risk of bias were not fulfilled but the report referred to no substantial change in vital signs during the study; and present, when none of the previous data could be retrieved.

Patients were separated into three groups: those randomly assigned to AEDs at efficacious doses; those randomly assigned to AEDs at non-efficacious doses; and those randomly assigned to placebo. The term efficacious refers to the antiepileptic potency of AEDs shown in randomised trials, and not to their efficacy at the individual level (many patients randomly assigned to AEDs at efficacious doses did not respond to the drug). More specifically, AED doses approved in Europe or in the USA as adjunctive therapy for refractory epilepsy were deemed

efficacious against the form of epilepsy or seizure indicated in the respective licence. Non-approved doses or non-approved indications of a licensed AED, as well as AED doses of drugs that failed to reach the market or are still under development, were deemed efficacious when they proved significantly more efficacious than placebo in at least one parallel-group randomised trial.

Statistical analysis

Our primary endpoint was to compare the incidence of definite and probable SUDEP between patients receiving AEDs at efficacious doses and those receiving placebo. The secondary endpoints were the comparison of all SUDEP (possible, probable, or definite), cause of deaths other than SUDEP, and all causes of death between the same two groups. Sensitivity analyses consisted of doing the same analyses after pooling patients who received AEDs at non-efficacious doses with either those allocated to efficacious AED doses or those assigned to the placebo group. Additional analyses aimed to test the primary endpoint in randomised trials done in refractory partial epilepsy and refractory primary generalised tonic-clonic seizures separately, and for every AED assessed.

Our primary analysis used the Mantel-Haenszel exact method without zero-cell corrections for a stratified odds ratio (OR) and associated 95% CI, with exclusion of trials with no event. To our knowledge, this is the most appropriate and robust method to do meta-analysis of rare events,¹⁵ and it was used by the US Food and Drug Administration (FDA) to test the effect of AEDs on suicidality.¹⁶ We further tested the effect of zero-event trials using the Mantel-Haenszel risk difference and associated CI. 95% CI statistical significance was set at a two-sided type 1 error of 0.05. Calculations were done using R software (version 2.13.0) and the meta library.

We calculated the total number of patient-years of follow-up in all three groups of patients (efficacious doses, non-efficacious doses, and placebo), and the related incidence of definite or probable SUDEP, all SUDEP, other causes of death, and all deaths using the Poisson model. Because of missing information about the precise duration of follow-up in patients who prematurely withdrew from the trials, we arbitrarily deemed the average mean duration of treatment of these patients to be half that of the trial duration. We did sensitivity analyses in which we deemed that all withdrawals occurred either on the first or on the last day of the trial.

We compared the rate of definite or probable SUDEP between trials with a duration of 12 weeks or less and trials with a duration of more than 12 weeks, a threshold corresponding to the median duration of the selected trials. We further tested the potential interaction between treatment duration and our primary analysis using meta-regression weighted by the inverse of variance and modelling the logarithm of odds ratio as a linear function of treatment duration. We used additive component of

residual heterogeneity to take into account the diversity between trials, and restricted maximum likelihood estimation.

Role of the funding source

There was no funding source for this study. PR and SR had access to all of the data in the study and responsibility for the decision to submit for publication.

Results

Our search initially retrieved 6718 reports and eventually led to the identification of 112 eligible trials, including 106 (95%) in refractory partial epilepsy and six (5%) in refractory primary generalised tonic-clonic seizures (figure 1, webappendix p 3). According to our criteria, we could exclude a reporting bias for the occurrence of deaths in 97 (87%) of these 112 trials, whereas the possibility of such bias was judged unclear in six (5%), and present in nine (8%) trials (ie, non-reported death might have occurred in these trials, but this seemed unlikely within the framework of industry-sponsored regulatory randomised trials). To allow enough time for us to obtain the detailed narratives of the deaths from pharmaceutical companies, the final search date for trials was set as Dec 31, 2010. Between that date and Sept 1, 2011, only two new randomised trials fulfilling our criteria were published, neither of which has reported any participant's death.^{17,18}

The selected randomised trials assessed a total of 21224 patients and 5589 patient-years. 27 AEDs were used at 86 doses, eight (9%) of which did not prove to be efficacious (table 1). A total of 33 deaths occurred in 19 (17%) of the trials (table 2). A specific cause of death other than SUDEP was well established in 13 patients, including traumatic shock, suicide, cerebral haemorrhage, pulmonary embolism, cerebral tumour, diabetic ketoacidosis, and intracerebral hypertension (table 2).

SUDEP was diagnosed in 20 patients and 14 (13%) trials (table 2).¹⁹⁻³² A detailed narrative of the circumstances of death was provided for 19 patients, including a transcription of the death certificate or post-mortem conclusions when available. 11 patients fulfilled the criteria of definite SUDEP,¹³ including unremarkable post-mortem data, with the exception of hypothermia in one patient and mild-to-moderate coronary atheroma in another.^{23,30} The patient with coronary atheroma was a 50-year-old married man with no past history of psychiatric disorder, who left his home as usual on the day preceding his death and was found dead in the street the next day at 9 am with hypothermia.²³ In view of the social status of the patient and absence of reason for not returning home at night, we believed that the only reasonable explanation is that the patient had unwitnessed SUDEP in the street, where his body developed hypothermia thereafter. The patient with coronary atheroma died suddenly while preparing for an electrocardiogram, with no indication of a preceding seizure.³⁰ Post-mortem examination did not disclose any

sign of myocardial infarction and concluded that death probably resulted from a non-documented cardiac arrhythmia. Within the context of active epilepsy, this narrative is fully consistent with the diagnosis of definite SUDEP.

Seven patients met the criteria for probable SUDEP, including one patient for whom a cardiac sudden death was also suspected in the original report.²⁸ This patient, with no history of ischaemic heart disease, suddenly lost consciousness in the street, fell down, and developed cyanosis; a doctor arrived soon after and noted that the patient was dead and cyanotic. Autopsy was not done, leading to the diagnosis of a probable SUDEP.

Finally, SUDEP was judged possible in two patients for which the autopsy revealed an undetermined amount of gastric content in the lung, suggesting the alternative diagnosis of aspiration. These two possible SUDEP occurred in patients receiving non-efficacious AED doses whose data were not used in primary analysis.^{31,32}

Ten (30%) of the 33 deaths, including three (15%) of the 20 SUDEP, occurred in the efficacious AED group, four (12%) deaths, including three (15%) SUDEP occurred in the non-efficacious AED group, and 19 (58%) deaths, including 14 (70%) SUDEP, occurred in the placebo group. SUDEP occurred from day 1 to day 192 following randomisation, with a mean delay of 77 (SD 69) days in the placebo group, 70 (SD 46) days in the efficacious treatment group, and 73 (SD 3) days in the non-efficacious treatment group.

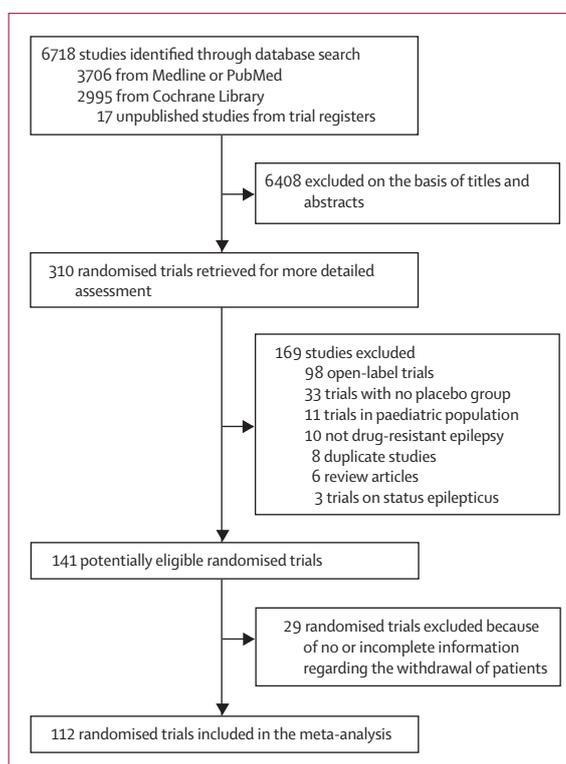


Figure 1: Study selection

The primary comparison of incidence of definite or probable SUDEP, between patients randomly assigned to AEDs at efficacious doses and those assigned to placebo, provided an OR of 0.17 (95% CI 0.05–0.57; $p=0.0046$), suggesting a greater risk of definite or probable SUDEP in patients allocated to placebo (table 3). Since all definite and probable SUDEP occurred in randomised trials of partial epilepsy and none in randomised trials of primary generalised tonic-clonic seizures, the findings were the same as for the overall results in the partial epilepsy trials but no OR could be calculated for definite and probable SUDEP in trials of primary generalised tonic-clonic seizures. The OR for every drug showed large

95% CI that overlapped with each other and always crossed an OR of 1 (webappendix p 7).

When comparing all SUDEP (possible, probable, and definite) between patients randomised to AEDs at efficacious doses and those receiving placebo, the OR was 0.17 (95% CI: 0.05–0.57; $p=0.0046$). The comparison of overall death rate between the same two groups provided an OR of 0.37 (0.17–0.81), suggesting a greater risk of death in patients receiving placebo ($p=0.0131$), whereas the comparison of non-SUDEP deaths showed an OR of 0.89 (95% CI 0.28–2.79; $p=0.84$; table 3).

Pooling data from the non-efficacious AED group with those from either the efficacious AED group or the

	Number of trials	Assessed doses		Efficacious doses		Non-efficacious doses		Placebo		Deaths during double-blind phase	
		Efficacious doses (mg/day)	Non-efficacious doses (mg/day)	Patients	Patient-years	Patients	Patient-years	Patients	Patient-years	All deaths	SUDEP
Refractory partial epilepsy											
Brivaracetam	1	5, 20, 50	..	154	20	54	7
Carisbamate	3	300, 400, 800, 1600	100, 200	698	170	482	115	484	114
Clobazam	2	30, 40	..	155	31	155	31
Clonazepam	1	2	..	20	3	20	3	1	..
Divalproex sodium	1	90 mg/kg	..	77	22	70	20
Eslicarbazepine acetate	4	400, 800, 1200	..	857	205	337	81	1	1
Felbamate	3	2300–3600	..	119	16	114	16
Ganaxalone	1	1875	..	24	0	27	0
Gabapentin	6	600, 900, 1200, 1800	..	695	157	400	92
Lacosamide	3	200, 400, 600	..	944	274	364	112
Lamotrigine	13	150, 200, 300, 400, 500, 700	..	888	300	583	177	2	2
Lamotrigine-xr	1	200–500	..	121	39	122	41
Levetiracetam	9	1000, 2000, 3000, 4000	..	1067	317	643	190	3	1
Levetiracetam-xr	1	1000	..	79	17	79	17
Lorazepam	1	2	..	10	1	10	1
Losigamone	2	1200, 1500	..	278	51	189	34	1	1
Oxcarbazepine	2	600, 1200, 2400	..	572	214	224	81	6	3
Pregabalin	5	150, 300, 450, 600	50	1060	216	88	19	427	91
Remacemide	5	800, 1200	300, 600	158	35	311	68	202	37	6	5
Retigabine	3	600, 900, 1200	..	816	221	427	127	4	1
Rufinamide	4	400, 800, 1600, 3200	200	744	160	127	27	496	112	3	1
Talampanel	1	25, 60, 75	..	49	12	49	12
Tiagabine	5	16, 32, 56, 64	..	581	171	363	107
Topiramate	10	200, 300, 400, 600, 800, 1000	..	849	245	454	136	1	1
Vigabatrin	13	1000, 2000, 3000, 4000, 6000	..	629	172	626	159	1	..
Sodium valproate	1	1200	..	20	3	20	3
Zonisamide	5	300, 400, 500, 600	100	494	140	57	25	398	115	3	3
Refractory primary generalised tonic-clonic seizures											
Gabapentin	1	..	1200	58	16	71	18	1	1
Lamotrigine	2	75, 150; 375	..	84	23	85	24
Levetiracetam	2	3000	..	142	50	144	50
Topiramate	1	6 mg/kg	..	39	11	41	10
All trials											
Total	112	12423	3297	1123	270	7678	2022	33	20

SUDEP=sudden unexpected death in epilepsy. xr=extended release.

Table 1: Main characteristics of included trials by antiepileptic drug

placebo group did not affect the findings (table 3). Similarly, sensitivity analyses which incorporated zero-event trials showed the same significant findings between groups (table 3). Simulations indicated that five additional trials each with one SUDEP in the efficacious AED group and none in the placebo group would be needed to invalidate our findings, which is unlikely to occur because only two of the 112 randomised trials done in the past 50 years reported such a finding.

The incidences of definite or probable SUDEP were 0·9 (95% CI 0·2–2·7) per 1000 person-years for patients randomly allocated to efficacious AED doses, 6·9 (3·8–11·6) for patients allocated to placebo, and 3·7 (0·1–20·6) in the non-efficacious AED population (table 4). When pooling all SUDEP (possible, probable, and definite), incidences only changed for inefficacious AED doses, with a value of 11·1 (2·3–32·4; table 4). Table 4 shows the incidence of non-SUDEP deaths and overall

	Study group	Cause of death	Autopsy	Details
Boas et al ¹⁹	Placebo	SUDEP, definite	Yes	Found dead at home; post-mortem examination showed congested lungs
Schachter et al ²⁰	Placebo	SUDEP, definite	Yes	Found dead at home; post-mortem examination unremarkable
Barcs et al ²¹	Placebo	SUDEP, definite	Yes	Found dead at home face down in pillow; post-mortem examination showed signs of terminal asphyxia
Barcs et al ²¹	Placebo	SUDEP, definite	Yes	Found dead at home; post-mortem examination showed only bitten tongue and bloody face
Richens et al ²²	Placebo	SUDEP, definite	Yes	Found dead in bed; post-mortem examination unremarkable
Richens et al ²²	Placebo	SUDEP, definite	Yes	Found dead, having been mowing his lawn; post-mortem examination unremarkable apart from an old subdural scar
Elger et al ²³	Placebo	SUDEP, definite	Yes	Found dead in the street; post-mortem examination unremarkable apart from severe hypothermia*
Sackellares et al ²⁴	Placebo	SUDEP, probable	No	Found dead in bed with face down in pillow
Brodie et al ²⁵	Placebo	SUDEP, probable	No	Found dead in bed with signs of a recent tongue bite
Brodie et al ²⁶	Placebo	SUDEP, probable	No	Found dead in bed
Brodie et al ²⁷	Placebo	SUDEP, probable	No	Found dead at home
Bauer et al ²⁸	Placebo	SUDEP, probable	No	Sudden death in the street was witnessed; cyanosis was reported
Brodie et al ²⁷	Placebo	SUDEP, probable	No	Found dead in bedroom by parents alerted by unusual noise; no sign of external trauma but seizure-related suffocation suspected
Cereghino et al ²⁹	Placebo	SUDEP, probable	No	Death described as sudden and unexpected according to the original report (no additional sponsor data available)
Kerr et al ³⁰	Topiramate 200 mg/day†	SUDEP, definite	Yes	Sudden death was witnessed while preparing for an electrocardiogram; post-mortem examination showed moderate coronary atheroma without infarction
Barcs et al ²¹	Oxcarbazepine 600 mg/day†	SUDEP, definite	Yes	Found dead; post-mortem report concluded that death resulted from a seizure
Chadwick et al ³¹	Remacemide 1200 mg/day†	SUDEP, definite	Yes	Found unconscious at home with no respiration or heart rate; cardiac output transiently restored by resuscitation; post-mortem examination showed evident pulmonary oedema, brain swollen, and profound cerebral hypoxia
Chadwick et al ³²	Gabapentin 1200 mg/day in PGTCS‡	SUDEP, possible	Yes	Post-ictal death witnessed; post-mortem examination showed congested lungs and aspirated gastric content§
Chadwick et al ³¹	Remacemide 600 mg/day‡	SUDEP, definite	Yes	Died after a sudden collapse and fall; post-mortem examination showed moderate coronary atheroma
Chadwick et al ³¹	Remacemide 600 mg/day‡	SUDEP, possible	Yes	Died after a seizure; post-mortem examination showed congested lungs and aspirated gastric content§
Boon et al ³³	Placebo	Car accident	No	Car passenger, hit by another vehicle
Boon et al ³³	Placebo	Car accident	No	Car driver, hit by another vehicle¶
French et al ³⁴	Placebo	Traumatic shock	No	Seizure-related fall that resulted in a large pneumothorax, collapse of lung, and death
Porter et al ³⁵	Placebo	Traumatic shock	No	Patient was assaulted and beaten to death
Mikkelsen et al ³⁶	Placebo	Cerebral tumour	No	..
Brodie et al ²⁵	Rufinamide 3200 mg/day†	Cerebral oedema	No	Past-history of intracranial hypertension, developed spastic ileus, fever, and brain herniation
Brodie et al ²⁵	Rufinamide 3200 mg/day†	Traumatic shock	No	Fall from the roof for unknown reason
French et al ³⁴	Retigabine 1200 mg/day†	Diabetic ketoacidosis	Yes	Past history of diabetes and obesity
Barcs et al ²¹	Oxcarbazepine 600 mg/day†	Cerebral haemorrhage	No	Non-traumatic massive brain haemorrhage that originated from the left caudate nucleus
Barcs et al ²¹	Oxcarbazepine 600 mg/day†	Traumatic shock	Yes	Motorcycle accident with multiple heart muscle and aorta ruptures
Barcs et al ²¹	Oxcarbazepine 2400 mg/day†	Pulmonary embolism	No	While bedridden after a hip and wrist fracture, patient developed nausea, sweating, and dyspnoea, and then died
Dodrill et al ³⁷	Vigabatrin 3000 mg/day†	Suicide	No	..
Chadwick et al ³¹	Remacemide 600 mg/day‡	Suicide	Yes	Death caused by a hand-gun wound in the head; past history of suicidal episodes and depression

PGTCS=primary generalised tonic-clonic seizures. SUDEP=sudden unexpected death in epilepsy. AED=antiepileptic drug. *The only reasonable explanation for this death was an unwitnessed SUDEP (see text for more details). †Anti-epileptic treatment regarded as efficacious against seizure. ‡Anti-epileptic treatment considered non-efficacious against seizure (including gabapentin 1200 mg in primary generalised tonic-clonic seizures). §Depending on the volume of gastric content recorded in the lungs, the cause of death is deemed SUDEP (small volume) or aspiration (large volume). Because this information was missing, we classified the death as possible SUDEP. ¶Death was wrongly allocated to the AED treatment group in the original report of this cross-over study, and was shifted to the placebo group by the study sponsor.

Table 2: Detailed characteristics of deaths by study

	Exact Mantel-Haenszel OR, zero-event trials excluded				Mantel-Haenszel RD, zero-event trials included			
	Number of trials	OR (95% CI)	p value	I ² (% 95% CI)*	Number of trials	RD (95% CI)	p value	I ² (% 95% CI)*
Primary analysis: efficacious AED doses vs placebo								
Definite and probable SUDEP (primary endpoint)	12	0.17 (0.05–0.57)	0.0046	0 (0–35.3)	109†	–0.0014 (–0.002 to 0)	0.0065	0 (0–0)
Definite, probable, and possible SUDEP	12	0.17 (0.05–0.57)	0.0046	0 (0–35.3)	109†	–0.0014 (–0.002 to 0)	0.0065	0 (0–0)
Other causes of death (non-SUDEP)	7	0.89 (0.28–2.79)	0.8407	0 (0–72.4)	109†	0 (0–0)	0.8467	0 (0–0)
All causes of death	17	0.37 (0.17–0.81)	0.0131	0 (0–29.8)	109†	–0.0015 (–0.003 to 0)	0.0226	0 (0–0)
Sensitivity analysis: efficacious and non-efficacious AED doses vs placebo								
Definite and probable SUDEP	13	0.14 (0.04–0.47)	0.0012	0 (0–26.4)	112	–0.0016 (–0.003 to 0)	0.0022	0 (0–0)
Definite, probable, and possible SUDEP	14	0.24 (0.09–0.64)	0.0044	0 (0–32.5)	112	–0.0014 (–0.003 to 0)	0.008	0 (0–0)
Other causes of death (non-SUDEP)	8	0.97 (0.32–2.98)	0.9599	0 (0–64.8)	112	0 (0–0)	0.9608	0 (0–0)
All causes of death	19	0.43 (0.21–0.87)	0.0184	0 (0–32.2)	112	–0.0014 (–0.003 to 0)	0.0288	0 (0–0)
Sensitivity analysis: efficacious AED doses vs placebo and non-efficacious AED doses								
Definite and probable SUDEP	12	0.20 (0.07–0.67)	0.0091	0 (0–35.4)	109†	–0.0013 (–0.002 to 0)	0.0093	0 (0–0)
Definite, probable, and possible SUDEP	12	0.19 (0.06–0.64)	0.0078	0 (0–27.2)	109†	–0.0014 (–0.002 to 0)	0.0071	0 (0–0)
Other causes of death (non-SUDEP)	7	0.79 (0.31–2.01)	0.6279	0 (0–72.2)	109†	0 (0–0)	0.8467	0 (0–0)
All causes of death	17	0.38 (0.17–0.81)	0.0129	0 (0–21)	109†	–0.0015 (–0.003 to 0)	0.0187	0 (0–0)

AED=antiepileptic drug. SUDEP=sudden unexpected death in epilepsy. OR=odds ratio. RD=risk difference. *I² statistic quantifies heterogeneity between studies on a scale of 0% to 100%. Large heterogeneity is usually denoted by I² values of 75% or more. †Three of the 112 eligible trials in which the active treatment group included only non-efficacious AED doses were excluded from this analysis, since they did not allow patients randomly assigned to placebo to be compared with those allocated to AED at efficacious doses.

Table 3: Risk of death according to the allocated treatment groups

deaths, and the sensitivity analyses of the effect of different treatment duration calculations for early withdrawals. The incidence of probable or definite SUDEP was similar for the 59 randomised trials with a duration of 12 weeks or less (3.2 per 1000 person-years, 95% CI 0.1–6.3), and for the 53 randomised trials of longer duration (3.2 per 1000 person-years, 1.4–5.1). Furthermore, duration of the trials did not interact with our primary analysis ($p=0.37$).

Discussion

This meta-analysis shows that adult patients with refractory epilepsy enrolled in double-blind randomised trials of add-on AEDs are less likely to die of a SUDEP if allocated to AEDs at efficacious doses rather than if allocated to placebo. To the best of our knowledge, this post-hoc analysis offers the first controlled evidence that an intervention may modify the risk of SUDEP.

Addressing the issue of SUDEP in the setting of double-blind randomised trials in epilepsy is challenging, because of the small scale and short-duration trials and the low rate of SUDEP. Indeed, one or more cases of SUDEP occurred in only 13% of the eligible randomised trials, leading to a majority of zero-event trials. This represents a well known limitation of meta-analysis for which several solutions are proposed,¹⁵ such as those used by the FDA to assess AED-related suicidality,¹⁶ which we applied in this study. In any event, the more than seven-fold difference in SUDEP incidence noted between patients randomly assigned to placebo and those receiving AEDs at efficacious doses points to a significant finding with magnitude that cannot be ignored.

A few patients (5%) were randomly assigned to AED doses that were judged to be non-efficacious on the basis of conservative, yet disputable, criteria. Nevertheless, pooling their data with those from patients allocated to either efficacious AED doses or placebo did not change our findings. The classification of type of death represents another issue that was easily settled in most patients with either a clear-cut cause of death other than SUDEP or data fulfilling the criteria of definite or probable SUDEP. Some doubt might be cast on the classification of two deaths as possible SUDEP, but these data were considered in only secondary analyses and proved not to modify our findings.

SUDEP incidence in prospective series of refractory partial epilepsy ranges from 3.5 to 9.3 per 1000 person-years.³ The population most similar to that assessed in our study was assessed in meta-analyses that investigated SUDEP rate in AED development programmes.^{38,39} Although these meta-analyses combined data from various types of trials, they portray the incidence of SUDEP mainly in open-label add-on studies in refractory partial epilepsy, including post-randomised trials extension studies. SUDEP rates were consistent in these studies, ranging from 3.2 to 4.2 per 1000 person-years,^{38,39} with the largest series providing a 95% CI of 2.9–5.0.³⁹ Thus, the SUDEP incidence recorded in patients allocated to efficacious AED doses during the double-blind phase of randomised trials seems to be the lowest recorded in refractory epilepsy (0.9 per 1000 person-years),³ with no overlap of 95% CI (0.2–2.7) with that of the open-label add-on studies.³⁹ However, direct comparison of figures between meta-analyses that have used different methods and only partly overlapping populations remains difficult.

Furthermore, the management of adjunctive AEDs is generally characterised by more flexible and lower mean doses during open-label extension studies than during randomised trials.

In our view, the most probable explanation for the very low SUDEP rate recorded in patients allocated to AEDs at efficacious doses during the blinded phase of randomised trials is the treatment-related reduction in seizure frequency. Indeed, several case-controlled series^{4,7,9} have shown that seizure frequency is a risk factor for SUDEP, although this finding seems to apply mainly to secondary generalised tonic-clonic seizures.^{3,8} However, we could not directly test this hypothesis because of missing information about change in seizure frequency in patients who had SUDEP during randomised trials.

Some patients or their carers might also take specific precautions while participating in a double-blind randomised trial, including better compliance or reinforced supervision, which might reduce the risk of SUDEP.⁴ However, these precautions should have applied to all randomised patients, and this outcome was not evident in the high SUDEP incidences noted in the non-efficacious AED and placebo groups. Indeed, the SUDEP incidence recorded in patients with uncontrolled seizures allocated to placebo (6.9 per 1000 person-years) was in the highest range of those previously reported in refractory epilepsy^{3,6} and about twice that recorded in open-label add-on AED studies,^{38,39} raising the question of whether their participation in randomised trials increased risk of SUDEP. Patients often agree to be enrolled in a double-blind randomised trial because of a worsening of their seizure disorder that would otherwise require an adaptation of their antiepileptic treatment. Placing these patients in a situation in which they will be denied a revision of their treatment during several months might increase their risk of SUDEP. Some patients might also withdraw one of their baseline AEDs to fulfil the inclusion criteria of add-on randomised trials, a decision that might further increase the risk of seizure aggravation and SUDEP. We cannot verify these hypotheses, but believe they represent important safety concerns that will need to be addressed in the future. Meanwhile, revision of the present framework of AED development programmes might be wise,⁴⁰ to avoid prolonged exposure to placebo or ineffective treatment when seizure control does not improve or even worsens.

Our findings offer hope and guidance in the prevention of SUDEP by indicating that an intervention can reduce the incidence of this devastating outcome. The risk-to-benefit ratio of adjunctive AEDs in refractory epilepsy is generally perceived as low, because of very low rates of long-term seizure freedom,^{41,42} disputable clinical relevance of an incomplete reduction in seizure frequency, and frequent side-effects,⁴³ leading some patients and physicians to withhold treatment revision despite uncontrolled seizures. Furthermore, results from case-controlled studies have shown that the greater the number of prescribed AEDs, the greater the

	Placebo	AED at efficacious doses	AED at non-efficacious doses
Primary analysis: mean time to early withdrawal occurred at mid-point of the trial			
Definite and probable SUDEP	6.9 (3.8–11.6)	0.9 (0.2–2.7)	3.7 (0.1–20.6)
Definite, probable, and possible SUDEP	6.9 (3.8–11.6)	0.9 (0.2–2.7)	11.1 (2.3–32.4)
Other causes of death (non-SUDEP)	2.5 (0.8–05.8)	2.1 (0.9–4.4)	3.7 (0.1–20.6)
All causes of death	9.4 (5.7–14.7)	3.0 (1.5–5.6)	14.8 (4.0–37.9)
Sensitivity analysis: all early withdrawals occurred on the first day of the trial			
Definite and probable SUDEP	7.4 (4.0–12.4)	1.0 (0.2–3.0)	3.9 (0.1–21.6)
Definite, probable, and possible SUDEP	7.4 (4.0–12.4)	1.0 (0.2–3.0)	11.7 (2.4–34.1)
Other causes of death (non-SUDEP)	2.6 (0.9–06.2)	2.4 (1.0–4.9)	3.9 (0.1–21.6)
All causes of death	10.1 (6.1–15.7)	3.4 (1.6–6.3)	15.5 (4.2–39.8)
Sensitivity analysis: all early withdrawals occurred on the last day of the trial			
Definite and probable SUDEP	6.5 (3.5–10.9)	0.8 (0.2–2.4)	3.5 (0.1–19.7)
Definite, probable, and possible SUDEP	6.5 (3.5–10.9)	0.8 (0.2–2.4)	10.6 (2.2–31.0)
Other causes of death (non-SUDEP)	2.3 (0.8–05.4)	1.9 (0.8–3.9)	3.5 (0.1–19.7)
All causes of death	8.8 (5.3–12.8)	2.7 (1.3–5.0)	14.1 (3.8–36.2)
Data are deaths per 1000 patient-years (95% CI). AED=antiepileptic drug. SUDEP=sudden unexpected death in epilepsy.			
Table 4: Incidence of death according to the allocated treatment groups			

risk of SUDEP.^{3,4,7–9} Although this association is most probably confounded by the relation between the number of AEDs and epilepsy severity, it might also discourage physicians from adding another AED to the baseline regimen of patients with refractory epilepsy. A recent meta-analysis⁸ further tested the effect of the frequency of generalised tonic-clonic seizures and polytherapy on the risk of SUDEP in the largest sample studied so far (289 cases and 958 controls). Whereas the OR for frequent generalised tonic-clonic seizures (≥ 3 seizures per year) as compared with no generalised tonic-clonic seizures was higher than 15 (95% CI 9.9–24.1), regardless of therapy, that for polytherapy compared with no treatment was only 1.95 (1.09–3.47), leading to the conclusion that the priority for prevention of SUDEP should be to minimise the number of generalised tonic-clonic seizures rather than to reduce the number of AEDs.⁸ Accordingly, our data suggest that add-on AEDs at doses effective on seizure frequency reduce the risk of SUDEP despite increasing the drug load, at least during the average 3-month duration of randomised trials. This finding provides an argument not only for active revision and optimum management of treatment in patients with uncontrolled seizures, but also for further prospective and long-term investigation of this unsettled issue. Indeed, the benefit of adjunctive AEDs on the risk of SUDEP might well decrease over time, at a pace that remains to be determined. The magnitude of the effect size reported in this meta-analysis indicates that a 1-year follow-up of a few thousand patients could be sufficient for the effective testing of an anti-SUDEP intervention, a feasible objective considering the prevalence of refractory epilepsy and the major concern shared by the epilepsy community regarding SUDEP.^{10,11}

Contributors

PR was responsible for generating the primary hypothesis and writing the first draft of the report. SR and PR were responsible for data collection and extraction. MC was responsible for building the statistical plan and models. All three authors contributed to the study design, interpretation of statistical analyses, writing, and revision of the report.

Conflicts of interest

PR has received speaker or consultant fees from Pfizer, GlaxoSmithKline, UCB Pharma, Eisai, and BIAL. SR has received speaker fees from Pfizer and UCB Pharma. MC declares that he has no conflicts of interest.

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