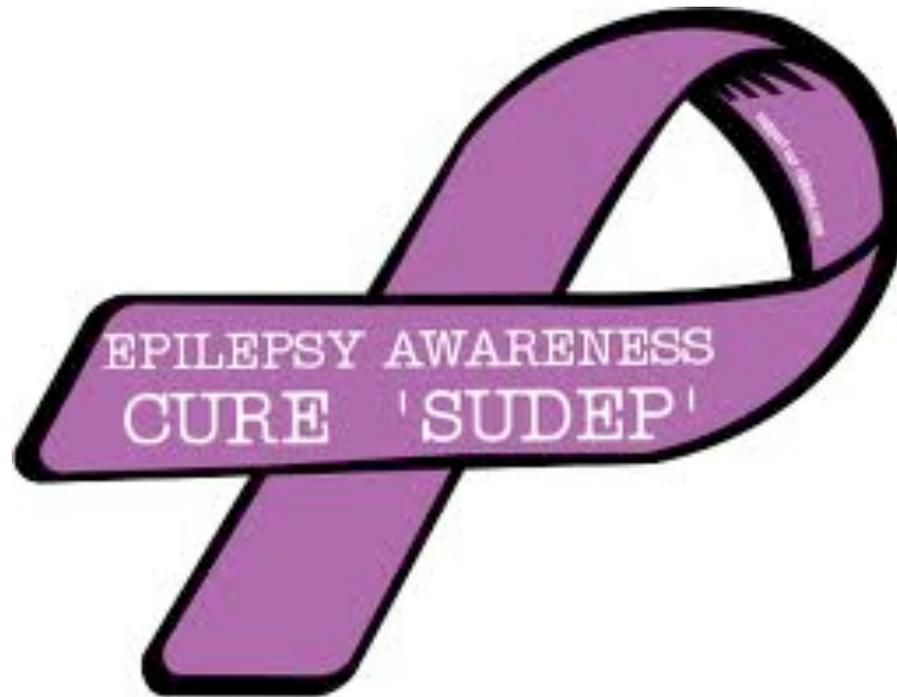


SUDEP:

Meta-analysis of randomized controlled trials



Adam Dickey, MD, PhD
PGY2 Neurology
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Recognizing and preventing epilepsy-related mortality

Rate of SUDEP estimated at around 1 per 1000 patient-years

300 million people = 3 million epileptics = ~ 3,000 Deaths annually

Similar to annual deaths from fire (2,760) and SIDS (1,575).

Devinsky Neurology 2015

SUDEP 2nd leading neurologic cause of lost years of life after stroke (and total epilepsy related mortality might be first).

Thurman Epilepsia 2014

A Finland study with 40 year follow-up showed a cumulative risk of SUDEP was as high as 12% in patients with childhood epilepsy

Sillanpaa NEJM 2010

Can SUDEP be prevented?

SUDEP actually associated with poly-therapy.

There is no clinical trial to assess effectiveness of SUDEP prevention.

SUDEP is so rare that getting a sufficient sample size is difficult.

Example:

If rate of SUDEP is 1 per 1,000, and my intervention lowers it to 0.5 per 1,000, would need to track 47,000 patients in each group for a year to achieve 80% power.

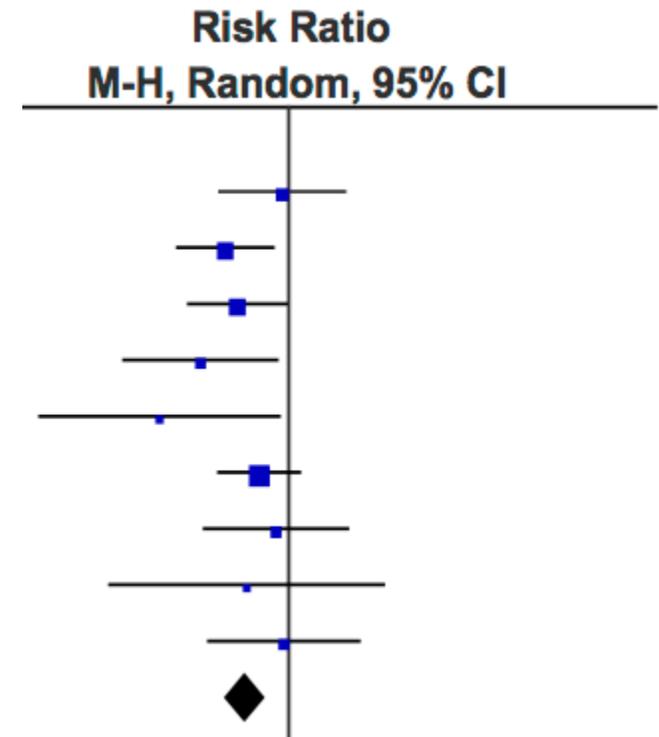
<https://select-statistics.co.uk/calculators/sample-size-calculator-two-proportions/>

Meta-analysis

A meta-analysis uses statistical methods to combine methods from multiple studies

They should give sufficient details of how studies were found, and how quality of studies were assessed (may use 2 reviews and give a kappa statistic)

Test for heterogeneity (such as inconsistency or I^2) to show if appropriate to pool, and display results as a forest plot.



Aspirin vs placebo:
Combined death, MI, or stroke

Raju, et al. 2011

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

Focused on refractory epilepsy, with higher rate of SUDEP – estimated 3.2 to 4.2 per 1000 patient years in open-label trials

Surveyed all double-blind, placebo controlled randomized trials of add-on AEDs with adults with uncontrolled epilepsy from 1960 to 2010.

112 trials included, with 21,224 patients and 5,589 patient-years.

33 deaths occurred, including 20 attributed to SUDEP (rate of SUDEP was 3.5 per 1000 patient-years.)

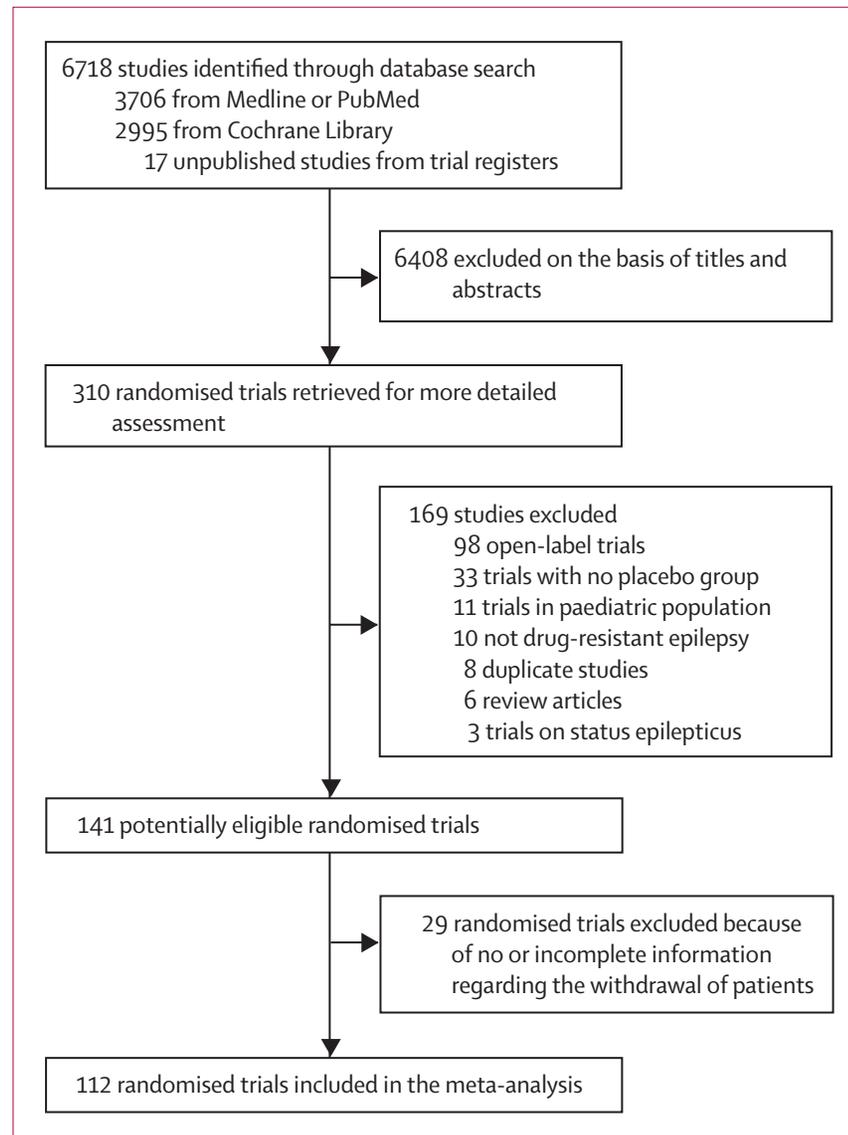


Figure 1: Study selection

	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
Ganaxone	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

Table 1: Main characteristics of included trials by antiepileptic drug

	Number of trials	Assessed doses		Efficacious doses		Non-efficacious doses		Placebo		Deaths during double-blind phase	
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Table 1: Main characteristics of included trials by antiepileptic drug

	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 PGTC§	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
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Table 2: Detailed characteristics of deaths by study

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Table 2: Detailed characteristics of deaths by study

SUDEP cases: **Placebo 14** **AED 3** **Non efficacious AED 3**

Results

OR 0.17 for SUDEP for AEDs vs. placebo (p=0.0046)

OR 0.37 for mortality for AEDs vs. placebo (p=0.013)

OR 0.89 for non-SUDEP death for AEDs vs. placebo (p=0.84)

Incidence for SUDEP 0.9 per 1000 patient-years for AED group
vs. 6.9 for placebo group

Limitations

Only applies to patients with refractory epilepsy, without standard definition

Treatment and comparison AEDs were variable

Incidences of SUDEP (0.9 vs. 6.9 per 1000 patient-years) was outside the range for refractory epilepsy previous estimated at 3.2 to 4.2 per 1000 patient years)

No data on seizure frequency (or type) in SUDEP pts– unknown if effect due to reduced seizure frequency.

Summary

Educate patients and families about risk of SUDEP (and epilepsy in general).

We seem justified in treating refractory epilepsy aggressively.

But what exactly qualifies as refractory epilepsy? One study required 4 partial seizures/month.

Barcs Epilepsia 2000

What should we do with refractory epilepsy suspected to be secondary to non-adherence, as this was an exclusion criteria?

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Barcs G, Walker EB, Elger CE, Scaramelli A, Stefan H, Sturm Y, Moore A, Flesch G, Kramer L, D Souza J. Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. *Epilepsia*. 2000 Dec 1;41(12):1597-607.

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