A SUDEP Journey

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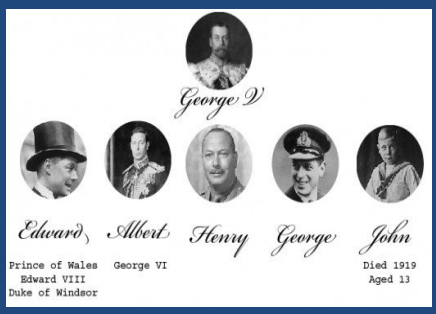
Patsy Custis

'She rose from dinner about four o' clock in better health and spirits than she appeared to have been for some time. Soon after which she was seized with one of her usual fits and expired in less than two minutes without uttering a word, a groan, or scare a sigh. This sudden and unexpected blow....has reduced my poor wife to the lowest ebb of misery.



Plan

- Incidence
- Risk factors
- Mechanisms

Irish perspective

Definition

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, where post-mortem examination does not reveal a cause for death.

Seizure 1998; 7: 355–358

The incidence of sudden unexpected death in epilepsy (SUDEP) in South Dublin and Wicklow

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Patients with epilepsy have a mortality rate higher than that of the general population. Some of this excess mortality is attributa to sudden unexpected death (SUDEP). We examined the incidence of this phenomenon both retrospectively and prospectiv in the population of South Dublin and Wicklow over the period May 1992–1995. Cases were ascertained by examination post-mortem registers of hospitals serving the area studied. Information on cases was sought from hospital records, gene practitioners and families. Fifteen cases (10 male, five female) were identified resulting in an overall incidence rate of SUD of 1:680/year for the 3 years of the study. This is the only study of incidence of SUDEP conducted in Ireland and our results in keeping with incidence rates elsewhere in Europe and the USA.

3 year period

- 18 death identified
- 15 SUDEP
- 10M 5F 14-59 years

Incidence of SUDEP

- Population – 681000
- Prevalence - 0.5%
- 1:680

Epilepsia, 51(5):845–852, 2010
doi: 10.1111/j.1528-1167.2009.02417.x

FULL-LENGTH ORIGINAL RESEARCH

Examining the prevalence of epilepsy and delivery of epilepsy care in Ireland

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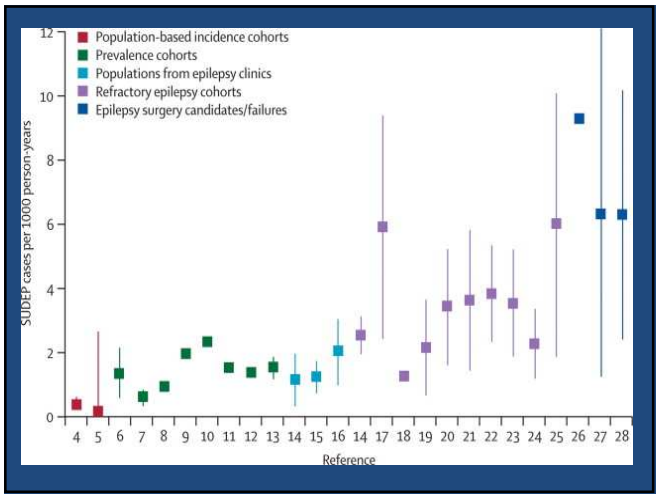
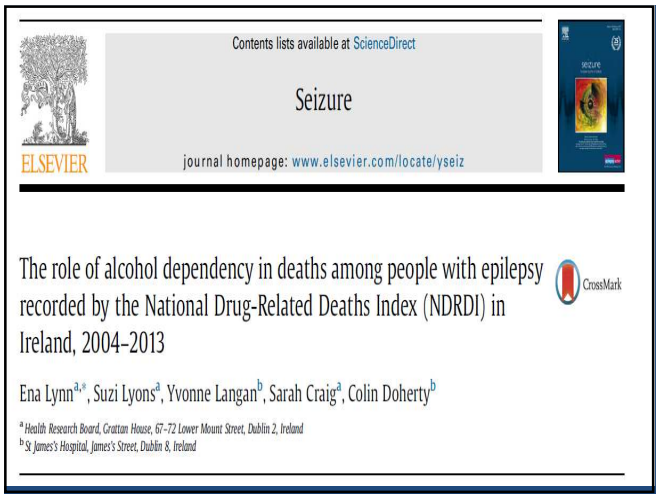


	Country	Study population	Case ascertainment	Cases (n)	Total person-years	SUDEP incidence (per 1000 person-years)
Ficker and co-workers[4]	USA	Community	Retrospective review of deaths in all epilepsy patients in Rochester (MN)	9	25 940	0·35
Lhatoo and co-workers[5]	UK	Community	Prospective follow-up of newly diagnosed epilepsy cohort	1	11 400	0·09
Jick and co-workers[6]	USA	AED prescription database, age 15–49 years	Retrospective review of deaths	11	8 460	1·3
Tennis and co-workers[7]	Canada	AED prescription database, age 15–49 years	Retrospective review of deaths	18	33 299	0·54
Terrence and co-workers[8]	USA	Community	Retrospective review of autopsy records in medical examiner's office	37	-	0·9
Leestma and co-workers[9]	USA	Community	Retrospective review of autopsy records in medical examiner's office	66	-	1·9
Leestma and co-workers[10]	USA	Community	Prospective ascertainment from medical examiner	60	-	2·3
Langan[11]	Ireland	Community	Retrospective review of autopsy records in coroner's office	15	-	1·5
Opeskin and co-workers[12]	Australia	Community	Prospective ascertainment from coroner's office	50	-	1·3

If information on actual number of person-years was not available, incidence was estimated on the basis of an assumed epilepsy prevalence of 0·5% in the population served by the medical examiner/coroner. AED=antiepileptic drug. –=not available.

Table 1: Community-based studies of the incidence of SUDEP


Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

The role of alcohol dependency in deaths among people with epilepsy recorded by the National Drug-Related Deaths Index (NDRDI) in Ireland, 2004–2013

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NDRDI

All deaths by drug or alcohol poisoning.

Deaths due to other causes in drug user those who are alcohol dependent.

- General Mortality Register
- Central Statistics Office
- Coroners' records
- HIPE
- National Methadone Treatment Register

2004 - 2013

- 225 deaths in those with a history of epilepsy
- 82 epilepsy main cause of death
- Majority SUDEP

- 75% male
- 26% illicit drug use
- 72% alcohol dependent
- 2/3 not alone at time of death
- Toxicology in 65, 2/3 no AED

Case-control study of SUDEP

Y. Langan, MB; L. Nashef, MD; and J.W. Sander, PhD

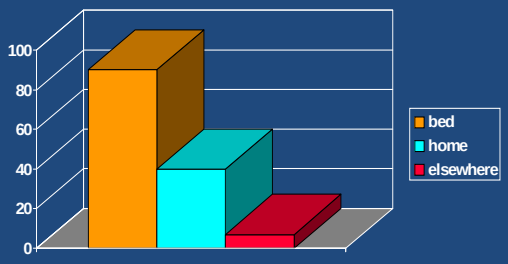
Abstract—*Objective:* To examine the influence of various factors on the risk of sudden unexpected death in epilepsy (SUDEP). *Methods:* The authors investigated 154 cases in which a postmortem examination was performed. Each case had four controls with epilepsy from the community, matched for age and geographic location. Backward stepwise conditional logistic regression analysis was performed and odds ratios for risk and protection were determined. *Results:* The risk of SUDEP was increased with a history of generalized tonic-clonic seizures in the previous 3 months (odds ratio [OR]: 13.8, 95% CI: 6.6 to 29.1). The presence of supervision at night was found to be protective (OR: 0.4, 95% CI: 0.2 to 0.8) when a supervising individual shared the same bedroom or when special precautions such as a listening device were employed (OR: 0.1, 95% CI: 0.0 to 0.3). *Conclusion:* This work lends support to the view that SUDEP is a seizure-related phenomenon and that control of tonic-clonic seizures is important in its prevention. Nocturnal supervision seems to protect against SUDEP.

NEUROLOGY 2005;64:1131–1133

Cases

- 154 cases
- 97 M 57 F
- Mean age 32 years
- 23 deaths witnessed

Location when found



Seizure Evidence

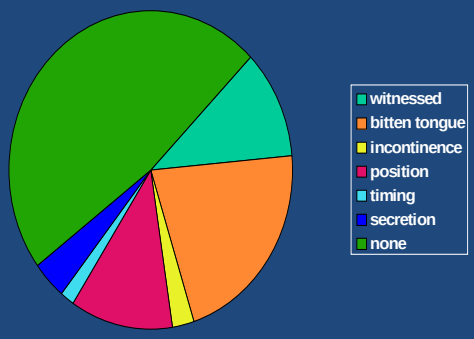


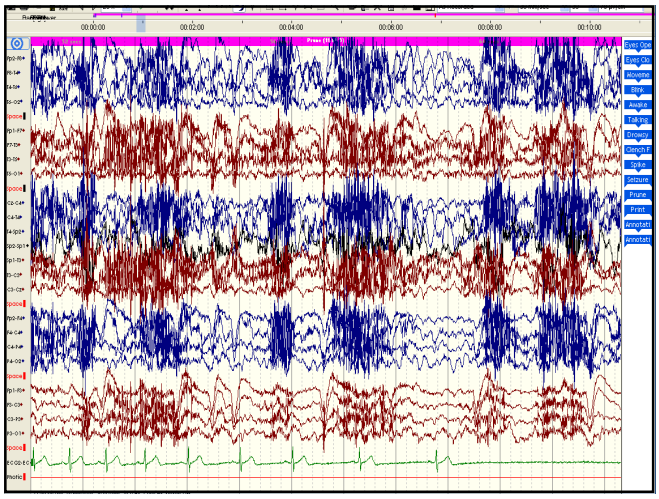
Table 2 Variables included in the model

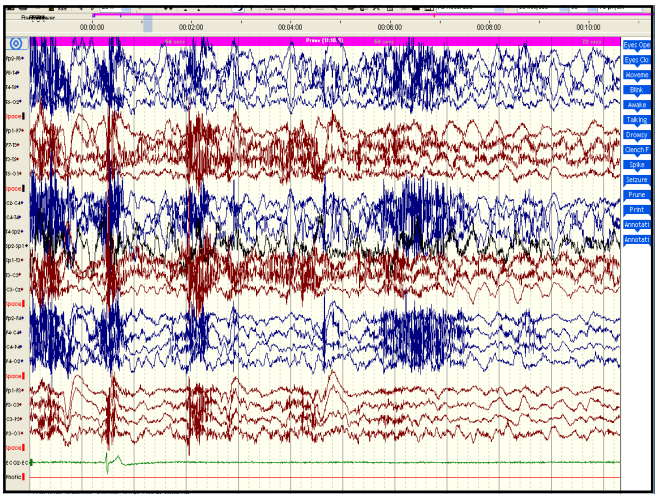
	No. of cases	Controls	OR	95% CI
History of generalized tonic-clonic seizures				
No	31	426	1	
Yes	120	108	13.8	6.6–29.1
No. of tonic-clonic seizures in previous 3 mo				
0–5	87	496	1	
6–10	17	13	0.7	0.2–2.5
11–20	13	2	19.4	1.7–226
21–50	7	3	14.6	1.3–165
>50	7	3	11.7	0.3–419
Total no. of AEDs ever				
1–2	42	400	1	
3–4	30	128	1.3	0.6–2.8
>4	47	50	3.1	1.4–7.0
0	14	12	21.7	4.4–106
Not known	21	26	8	2.7–25.6
Carbamazepine (current use)				
No	72	381	1	
Yes	74	235	2	1.1–3.8
Supervision				
None	109	169	1	
Same room	34	156	0.4	0.2–0.8
Special precautions	11	42	0.1	0.0–0.3
Asthma				
No	142	522	1	
Yes	6	67	0.2	0.1–0.9

AED = antiepileptic drug.

Why?

- Cardiac
- Respiratory
- Animal models



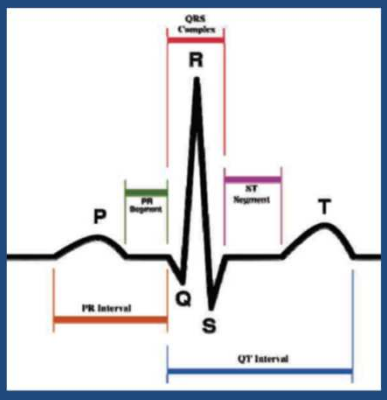


	Cause of epilepsy	EEG localisation	Drugs given	Seizure types	Number of seizures with data from implantable loop recorders (SPS/CPS and SGTCS)	Ictal heart rate (bpm; median [range])	Bradycardic episodes
Patient (sex, age [years])							
1 (F, 48)	Posterior SEH	Widespread	PH, TO, VG, LE	SPS, CPS	23 (4/19)	100 (25–140)	Ictal (25 bpm for 10 s)
2 (F, 31)	Bilateral HS	Bitemporal	GB	SPS, CPS	34 (34/0)	145 (95–175)	–
3 (M, 22)	Cryptogenic	Left TLE	CB, TO	SPS, CPS	13 (7/6)	115 (100–145)	–
4 (F, 32)	Bilateral HS	Right TLE	CB, PH, PB, CL	SPS, CPS	17 (2/15)	115 (100–140)	–
5 (M, 56)	Cryptogenic	Left TLE	LE	SPS, CPS	27 (1/26)	105 (85–140)	–
6 (F, 53)	Left frontal DNT	Left hemisphere	GB, OX, LE	SPS, CPS	28 (28/0)	120 (80–140)	–
7 (F, 45)	Bilateral HS	Right TLE	CB, PR, LE	CPS, SGTCS	22 (0/22)	102·5 (80–145)	EMB of 40 bpm
8 (M, 42)	Bilateral HS	Left TLE	TO, PH, LE, CL	SPS, CPS	33 (0/33)	120 (90–135)	Ictal (4·6 and 18 s asystole)
9 (M, 45)	Right HS	Right TLE	CB, GB, LE	SPS, SGTCS	9 (1/8)	105 (80–120)	14 s asystole
10 (M, 54)	Post-traumatic	Left hemisphere	CB, TO, CL	CPS	19 (0/19)	80 (65–100)	–
11 (F, 36)	Right HS and IGE	Right TLE	CB, TO, AC, AT	SPS, CPS, SGTCS	26 (4/22)	105 (30–145)	Ictal (30 bpm for 15 s and EMB of 35 bpm)
12 (F, 40)	Cryptogenic	Bifrontal	CB, LE	SPS, CPS	19 (0/19)	75 (40–105)	Ictal (40 bpm for 10 s)
13 (M, 49)	Cryptogenic	Bifrontal	CB, PH, LE	CPS, SGTCS	17 (0/17)	90 (70–120)	–
14 (F, 35)	Left HS	Bifrontal	CB, LM	CPS, SGTCS	30 (0/30)	110 (80–140)	–
15 (F, 39)	Cryptogenic	Bifrontal	VA, LM	SPS, CPS, SGTCS	13 (0/13)	105 (95–115)	–
16 (M, 24)	Perinatal injury	Left FLE	PH, OX, CL, LM	CPS, SGTCS	9 (0/9)	120 (90–125)	Ictal (5 s asystole and EMB of 35 bpm)
17 (M, 29)	Cryptogenic	Left FLE	CB, LE	CPS	4 (0/4)	102·5 (100–105)	–
18 (M, 36)	Left TL cavernoma	Left TLE	CB, CL	SPS, CPS, SGTCS	12 (0/12)	145 (90–170)	–
19 (M, 45)	Cryptogenic	Left TLE	CB, CN	CPS	22 (9/13)	105 (30–130)	Ictal (30 bpm for 30 s)
20 (F, 39)	Cryptogenic	Widespread	CB, LE	SPS, CPS, SGTCS	0 (0/0)	n/a (withdrew)	–

SEH=subependymal heterotopia (malformation of cortical development). SPS=simple partial seizure. CPS=complex partial seizure. SGTCS=secondarily generalised tonic-clonic seizure. HS=hippocampal sclerosis. DNT=dysembryoplastic neuroepithelial tumour. IGE=idiopathic generalised epilepsy. TLE=temporal lobe epilepsy. FLE=frontal lobe epilepsy. Bifrontal=bilateral frontal lobe epilepsy. Bitemporal=bilateral temporal lobe epilepsy. PH=phenytoin. TO=topiramate. CB=carbamazepine. CL=clobazam. GB=gabapentin. OX=oxcarbazepine. LE=levetiracetam. AC=acetazolamide. LM=lamotrigine. VA=valproate. VG=vigabatrin. PB=phenobarbital. PR=primidone. CN=clonazepam. AT=atenolol. EMB=early morning bradycardia. n/a=not applicable.

Table: Clinical characteristics and recorded data of patients with focal epilepsy

- Reduced HRV
- Baroreflex sensitivity



Long QT syndromes

- Transgenic mice
- Mutations co-expressed in heart and brain
- Cardiac arrhythmia, epilepsy, SUDEP

Journal of Neurology, Neurosurgery, and Psychiatry 1996;60:297–300

Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy

L Nashef, F Walker, P Allen, J W A S Sander, S D Shorvon, D R Fish

doi:10.1093/brain/awn277 *Brain* (2008), **131**, 3239–3245

Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors

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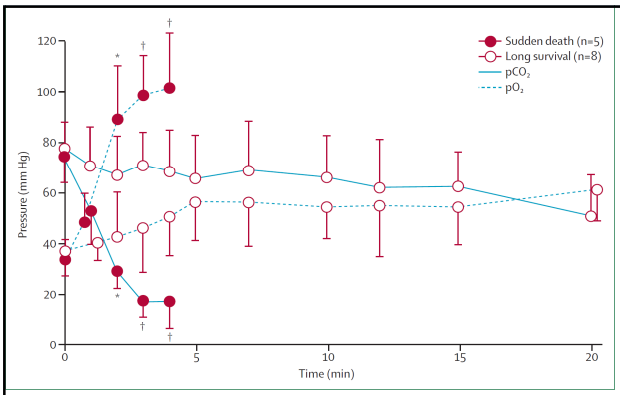


Figure 2: **pO_2 and pCO_2 concentrations during seizures in sheep**
In experimental status epilepticus in sheep, there is a rapid fall in pO_2 and rise in pCO_2 concentrations before death in animals that died (red circles) compared with those that survived (open circles) attributable to hypoventilation. Reproduced from Johnston and colleagues.[39] *p=0·01. †p=0·001. pO_2=partial pressure of oxygen. pCO_2=partial pressure of carbon dioxide. The error bars represent the standard error.

Neurotransmitters

- Adenosine
- Serotonin
- SIDS

Articles

Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study

Philippe Ryvlin, Lina Nashef, Samden D Lhatoo, Lisa M Bateman, Jonathan Bird, Andrew Bleasel, Paul Boon, Arielle Crespel, Barbara A Dworetzky, Hans Hegerhuren, Holger Lerche, Louis Maillard, Michael P Malter, Cecile Marchal, Jogarlapudi M K Murthy, Michael Nitsche, Ekaterina Pataraia, Terje Rabben, Sylvain Rheims, Bernard Sadzot, Andreas Schulze-Bonhage, Masud Seyal, Elson L So, Mark Spitz, Anna Szucs, Meng Tan, James X Tao, Torbjorn Tomson

Summary

Background Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in people with chronic refractory epilepsy. Very rarely, SUDEP occurs in epilepsy monitoring units, providing highly informative data for its still elusive pathophysiology. The MORTEMUS study expanded these data through comprehensive evaluation of cardiorespiratory arrests encountered in epilepsy monitoring units worldwide.

Methods Between Jan 1, 2008, and Dec 29, 2009, we did a systematic retrospective survey of epilepsy monitoring units located in Europe, Israel, Australia, and New Zealand, to retrieve data for all cardiorespiratory arrests recorded in these units and estimate their incidence. Epilepsy monitoring units from other regions were invited to report similar cases to further explore the mechanisms. An expert panel reviewed data, including video electroencephalogram (VEEG) and electrocardiogram material at the time of cardiorespiratory arrests whenever available.

Findings 147 (92%) of 160 units responded to the survey. 29 cardiorespiratory arrests, including 16 SUDEP (14 at night), nine near SUDEP, and four deaths from other causes, were reported. Cardiorespiratory data, available for ten cases of SUDEP, showed a consistent and previously unrecognised pattern whereby rapid breathing (18–50 breaths per min) developed after secondary generalised tonic-clonic seizure, followed within 3 min by transient or terminal cardiorespiratory dysfunction. Where transient, this dysfunction later recurred with terminal apnoea occurring within 11 min of the end of the seizure, followed by cardiac arrest. SUDEP incidence in adult epilepsy monitoring units was 5·1 (95% CI 2·6–9·2) per 1000 patient-years, with a risk of 1·2 (0·6–2·1) per 10 000 VEEG monitorings, probably aggravated by suboptimum supervision and possibly by antiepileptic drug withdrawal.

Interpretation SUDEP in epilepsy monitoring units primarily follows an early postictal, centrally mediated, severe alteration of respiratory and cardiac function induced by generalised tonic-clonic seizure, leading to immediate death or a short period of partly restored cardiorespiratory function followed by terminal apnoea then cardiac arrest. Improved supervision is warranted in epilepsy monitoring units, in particular during night time.

Funding Commission of European Affairs of the International League Against Epilepsy.

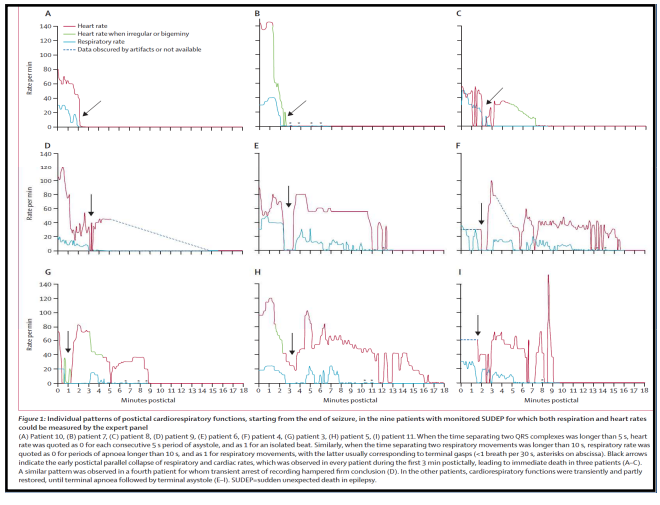
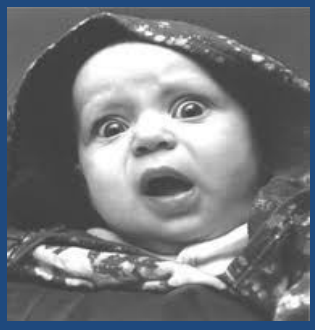


Figure 1: Individual patterns of postictal cardiorespiratory functions, starting from the end of seizure, in the nine patients with monitored SUDEP for which both respiration and heart rates could be measured by the expert panel
(A) Patient 10, (B) patient 7, (C) patient 8, (D) patient 9, (E) patient 6, (F) patient 4, (G) patient 3, (H) patient 5, (I) patient 11. When the time separating two QRS complexes was longer than 5 s, heart rate was quoted as 0 for each consecutive 5 s period of asystole, and as 1 for an isolated beat. Similarly, when the time separating two respiratory movements was longer than 10 s, respiratory rate was quoted as 0 for periods of apnoea longer than 10 s, and as 1 for respiratory movements, with the latter usually corresponding to terminal gasps (<1 breath per 30 s, asterisks on abscissa). Black arrows indicate the early postictal parallel collapse of respiratory and cardiac rates, which was observed in every patient during the first 3 min postictally, leading to immediate death in three patients (A–C). A similar pattern was observed in a fourth patient for whom transient arrest of recording hampered firm conclusion (D). In the other patients, cardiorespiratory functions were transiently and partly restored, until terminal apnoea followed by terminal asystole (E–I). SUDEP=sudden unexpected death in epilepsy.

Discussing SUDEP



Prevention of SUDEP

- Optimise seizure control

? supervision
? lattice pillows
? serotonin
? opiate and adenosine receptor inhibitors

???? Test an intervention

The Epilepsy Deaths Register for Ireland

Making every epilepsy death count

Epilepsy Ireland SUDEP Action UCC

What now?

- In collaboration with HRB collect all epilepsy deaths referred to the coroner.
- International case control study