13rd Epilepsy Course for Neurology and Pediatric Neurology Residents, 2022

SUDEP:
Sudden Unexpected Death in Epilepsy

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Disclosures

- No financial disclosures relevant to this talk

Overview

1. Define the increased risk of mortality & describe the causes in PWE
2. List the incidence rates of SUDEP in different epilepsy populations
3. List the modifiable & non-modifiable risk factors for SUDEP
4. Identify preventive strategies to reduce SUDEP risk

Mortality in Epilepsy

- Standardized Mortality Ratio (SMR): 2.2-2.6
- SMR higher for children: 5.3-9.0
- Predictors of mortality:
  - Active epilepsy
  - Symptomatic epilepsy
  - ASM adherence
  - Medical intractability

"*sudden death is 24X more likely in PWE[1]*"

- Deaths related to epilepsy: direct/indirect, SUDEP
- Deaths related to the cause of epilepsy
- Deaths unrelated to epilepsy

40-year follow-up of childhood-onset epilepsy: 24% mortality[2]

Table 2. Causes of Death.

Variable	All Subjects (N=245)	Subjects with Idiopathic or Cryptogenic Epilepsy (N=122)	Subjects with Epilepsy Due to Remote Symptomatic Causes (N=123)*
Total deaths — no.	60	15	45
Death related to epilepsy — no./total no. of deaths (%)	33/60 (55)	9/15 (60)	24/45 (53)
Witnessed seizure — no.	6	0	6
Status epilepticus — no.	4	0	4
Probable seizure — no.	3	2	1
Drowning — no.	6	0	6
Sudden, unexplained death — no.	18	7	11
Death not related to epilepsy — no./total no. of deaths (%)	26 (43)	6 (40)	20 (44)
Pneumonia — no.	12	0	12
Cardiovascular disease — no.	8	2	6
Suicide — no.	2	2	0
Other cause of death — no.	4	2	2
Cause of death unknown — no.	1	0	1

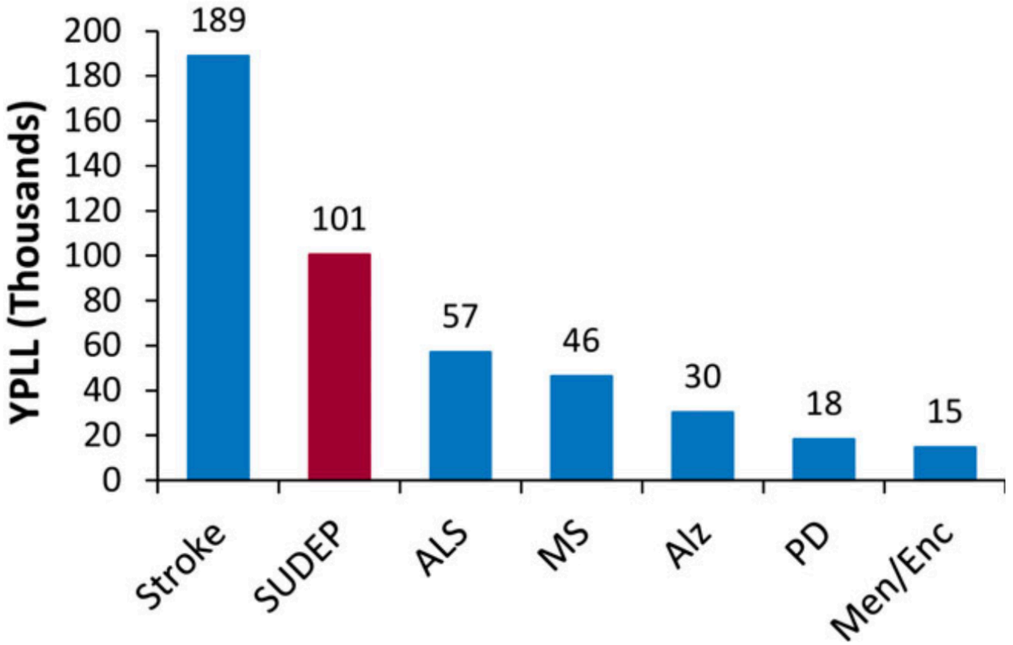
* A remote symptomatic cause of epilepsy indicates epilepsy associated with a major neurologic abnormality or insult.

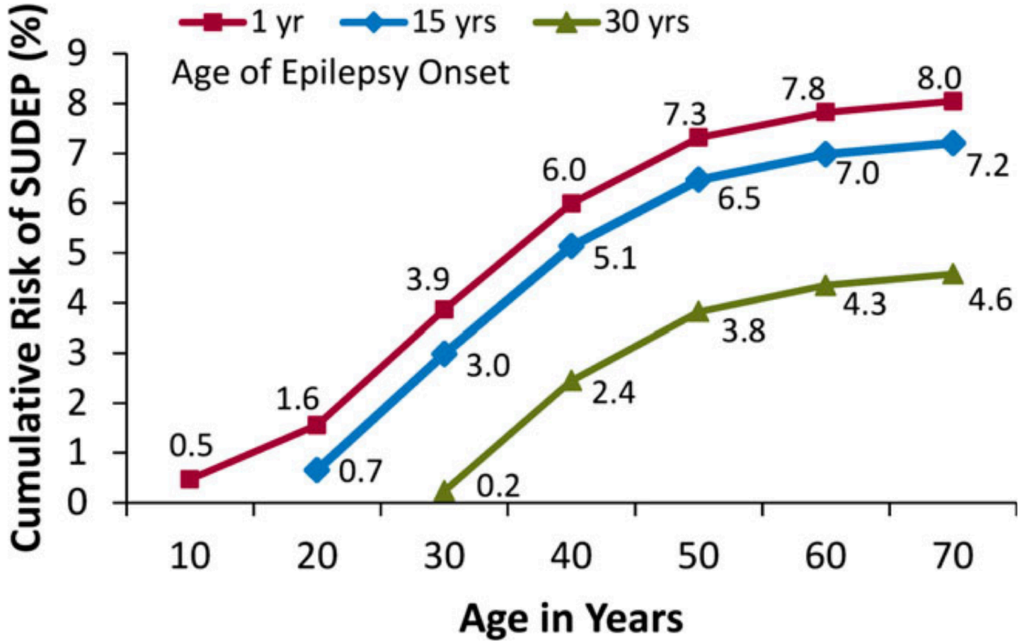
1. Ficker et al. *Neurology* 1998; 2. Sillapaa & Shinnar. *N Engl J Med* 2010; 3. Ficker. *Epilepsia* 2000

Sudden unexpected death in epilepsy: Assessing the public health burden

*David J. Thurman, †Dale C. Hesdorffer, and ‡Jacqueline A. French

Systematic search for epidemiologic studies of sudden death in epilepsy





- ✓ SUDEP ranks second only to stroke in term of years of potential life lost (YPLL)
- ✓ Epilepsy onset at age 1 yr: lifetime risk of 8.0% by age 70

Thurman et al. *Epilepsia* 2014

Unifying the definitions of sudden unexpected death in epilepsy

*Lina Nashef, †Elson L. So, ‡Philippe Ryvlin, and §Torbjörn Tomson

Epilepsia, 53(2):227–233, 2012

- ☑ Has epilepsy & death was unexpected, in benign circumstances
- ☑ NOT a consequence of trauma, drowning, or status epilepticus
- May be **witness *or* unwitnessed** ; evidence of a preceding seizure is NOT required
- Postmortem exam: NOT reveal cause of death = ***Definite*** SUDEP
- without autopsy = ***Probable*** SUDEP; a competing cause of death = ***Possible*** SUDEP
- Survives resuscitation >1 h = ***Near***-SUDEP
- A clear cause of death is known = **NOT** SUDEP

Scenarios

1) Sudden death in conjunction with witness first seizure; negative postmortem examination

2) Epilepsy; found dead in water but not submersed; postmortem exam does not show drowning

3) Patient with uncontrolled epilepsy; found dead in the daytime; postmortem reveals aspiration of gastric contents of unspecified amount

4) Epilepsy; cardiorespiratory arrest after witnessed sz; resuscitated but dies within a few days, negative postmortem examination

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society

Table 1 Conclusions for sudden unexpected death in epilepsy (SUDEP) incidence

Population	SUDEP/1,000 patient-years (confidence interval)	Confidence
Overall	0.58 (0.31–1.08)	Low
Childhood	0.22 (0.16–0.31)	Moderate
Adulthood	1.2 (0.64–2.32)	Low

Incidence

- Overall **1:1,700 pt-yrs**
- Children **1:4,500 pt-yrs**
- Adults **1:1,000 pt-yrs**

Table 2 Conclusions for sudden unexpected death in epilepsy (SUDEP) risk factors

Factor	OR (CI)	Confidence level
Presence of GTCS vs lack of GTCS	10 (17–14)	Moderate
Frequency of GTCS	OR 5.07 (2.94–8.76) for 1–2 GTCS per year and OR 15.46 (9.92–24.10) for >3 GTCS per year	High
Not being seizure-free for 1–5 y	4.7 (1.4–16)	Moderate
Not adding an AED when patients are medically refractory	6 (2–20)	Moderate
Nocturnal supervision (risk reduction)	0.4 (0.2–0.8)	Moderate
Use of nocturnal listening device (risk reduction)	0.1 (0–0.3)	Moderate

No increase risk associated with ASM polytherapy or any individual ASM

Incidence of sudden unexpected death in epilepsy in children is similar to adults

Anne E. Keller, MPH, Robyn Whitney, MD, Shelly-Anne Li, MSc, Michael S. Pollanen, MD, PhD, and Elizabeth J. Donner, MD, MSc

SUDEP is more common in children than previously reported

Table Incidence of SUDEP by analysis method as compared to reported incidence in the literature

Method	Included classifications of SUDEP	No. of SUDEP cases	Epilepsy prevalence, %	Incidence (95% CI) per 1,000 patient-years
Crude analysis	All	17	0.27	1.17 (0.68–1.88)
Canada	Definite, definite plus, probable	16	0.27	1.11 (0.63–1.79)
Sensitivity analysis	Definite, definite plus, probable	16	0.21	1.42 (0.81–2.31)
	Definite, definite plus, probable	16	0.34	0.88 (0.50–1.42)
Capture-recapture analysis	Definite, definite plus, probable	21	0.27	1.45 (0.90–2.22)

From the literature

Source	Included classifications of SUDEP	Population	Incidence (95% CI) per 1,000 patient-years
AAN guidelines[1]	Definite, definite plus,[a] probable	"Childhood"	0.22 (0.16–0.31)
	Definite, definite plus,[a] probable	"Adult"	1.22 (0.64–2.32)
Sveinsson et al.[2]	Definite, definite plus, probable	<16 y	1.11 (0.45–2.29)
Sweden	Definite, definite plus, probable	16–50 y	1.13 (0.76–1.62)
	Definite, definite plus, probable	>50 y	1.29 (0.88–1.82)

Keller et al. *Neurology* 2018

SUDEP in the North American SUDEP Registry

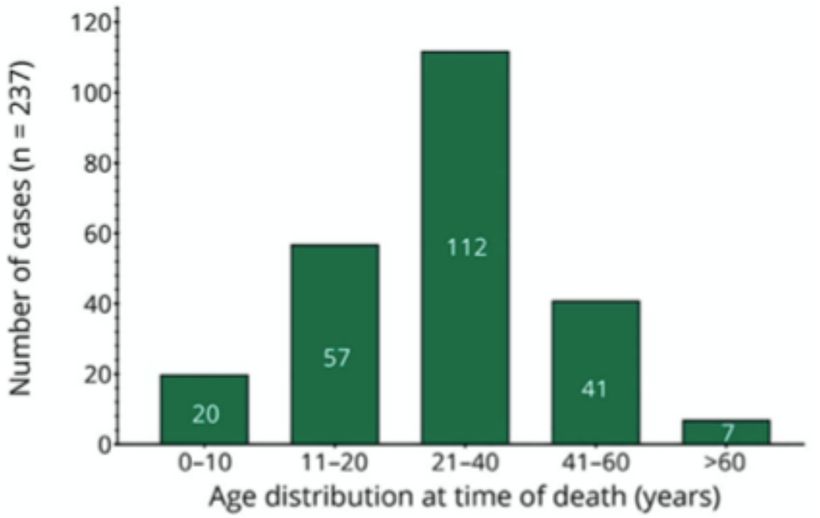
The full spectrum of epilepsies

Chloe Verducci, BA, Fizza Hussain, MS, Elizabeth Donner, MD FRCP(C), Brian D. Moseley, MD, Jeffrey Buchhalter, MD, Dale Hesdorffer, PhD, Daniel Friedman, MD, MSc, and Orrin Devinsky, MD

Table 1 Circumstances of death (n = 237)

Circumstance of death	n	N	%
Took last ASM dose?	66	180	37
Asleep at time of death	118	168	70
Known recent illness	30	175	17
Room sharing during sleep	57	161	35
CPR performed	108	212	51
Sleep deprived	24	157	15
Full autopsy performed	155	237	65
Found in prone position	128	186	69
Evidence of preceding seizure	123	167	74

Young adult, during apparent sleep, were prone



median age: 26 y (1-70)

- Low rate of witnessed death 7%
- *Only 16% of next of kin had heard about SUDEP before their relatives' death*

Verducci et al. *Neurology* 2019

SUDEP in the North American SUDEP Registry

The full spectrum of epilepsies

Chloe Verducci, BA, Fizza Hussain, MS, Elizabeth Donner, MD FRCP(C), Brian D. Moseley, MD, Jeffrey Buchhalter, MD, Dale Hesdorffer, PhD, Daniel Friedman, MD, MSc, and Orrin Devinsky, MD

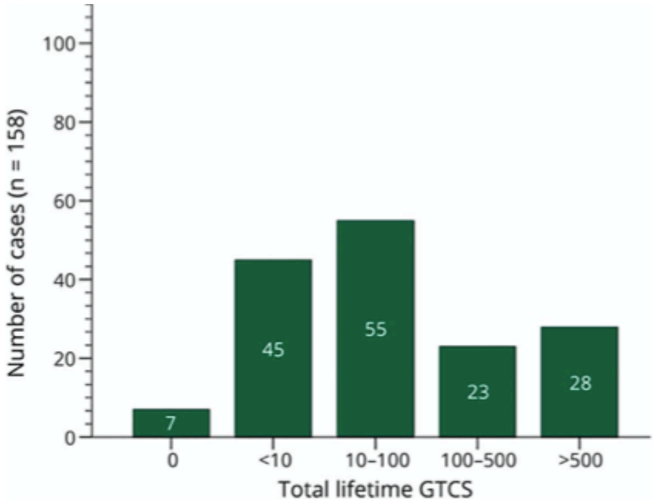
- SUDEP affects the full spectrum of epilepsies
- GGE are also at risk
- SUDEP risk is NOT limited to frequent GTCS

Table 3 Seizure histories in cases of SUDEP with sufficient information to adjudicate (143 of 237)

Seizure history	n	N	%
Generalized	57	143	40
Tonic-clonic	46	143	32
Focal	86	143	60
Focal to bilateral	67	143	47
Preserved awareness	20	143	14
Impaired awareness	59	143	41
Unclassified	94	237	40
Both	15	143	10

JME 9 (4%)
BECTS 4 (1%)
LGS 5 (3%)
Febrile Sz plus 7 (3%)
Dravet syndrome 13 (5%)
Dup15q chromosome 9 (4%)

Epilepsy surgery 42 (18%)
Neurostimulation 32 (14%)

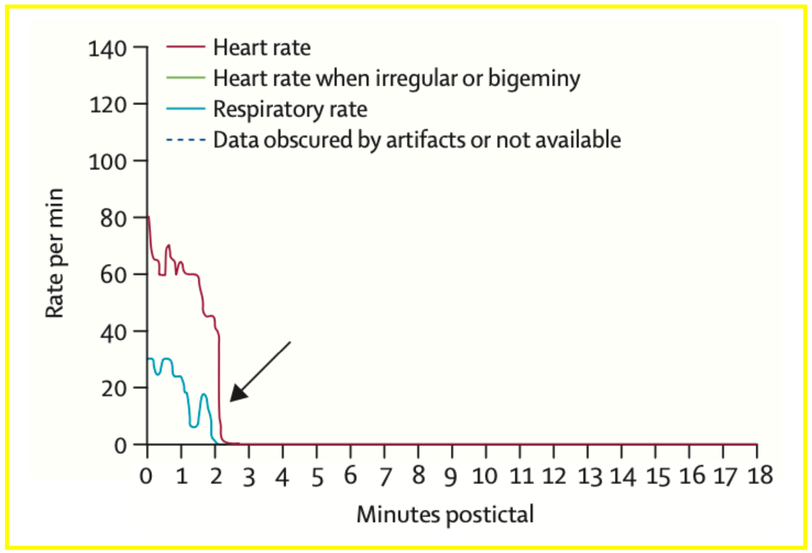


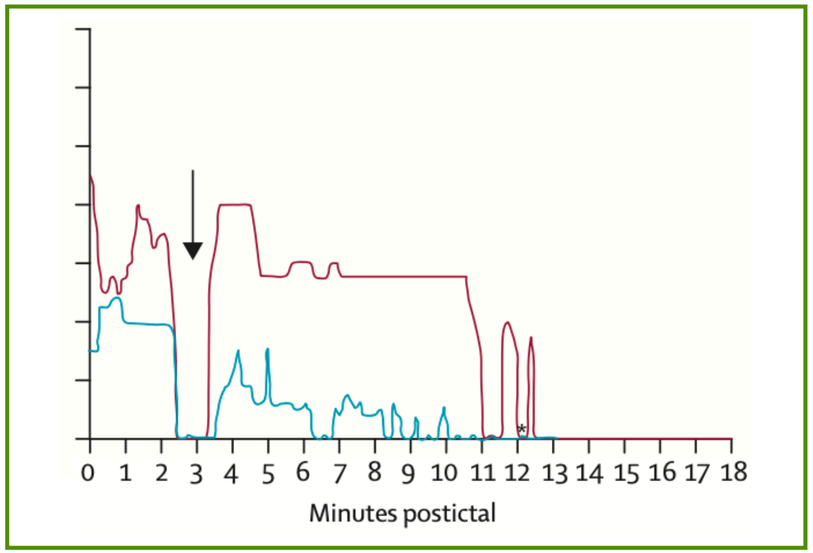
Verducci et al. *Neurology* 2019

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

Lancet Neurol 2013; 12: 966–77

- 147 units; 16 SUDEP (11 monitored), 9 near-SUDEP
- Early post-ictal tachypnea → cardiorespiratory arrest w/n 3 min ⇢ reversed ⇢ terminal apnea → terminal asystole; EEG finding: *PGES was observed in all*
- *Time to CPR*: SUDEP 13-180 min; near-SUDEP ≤3 min



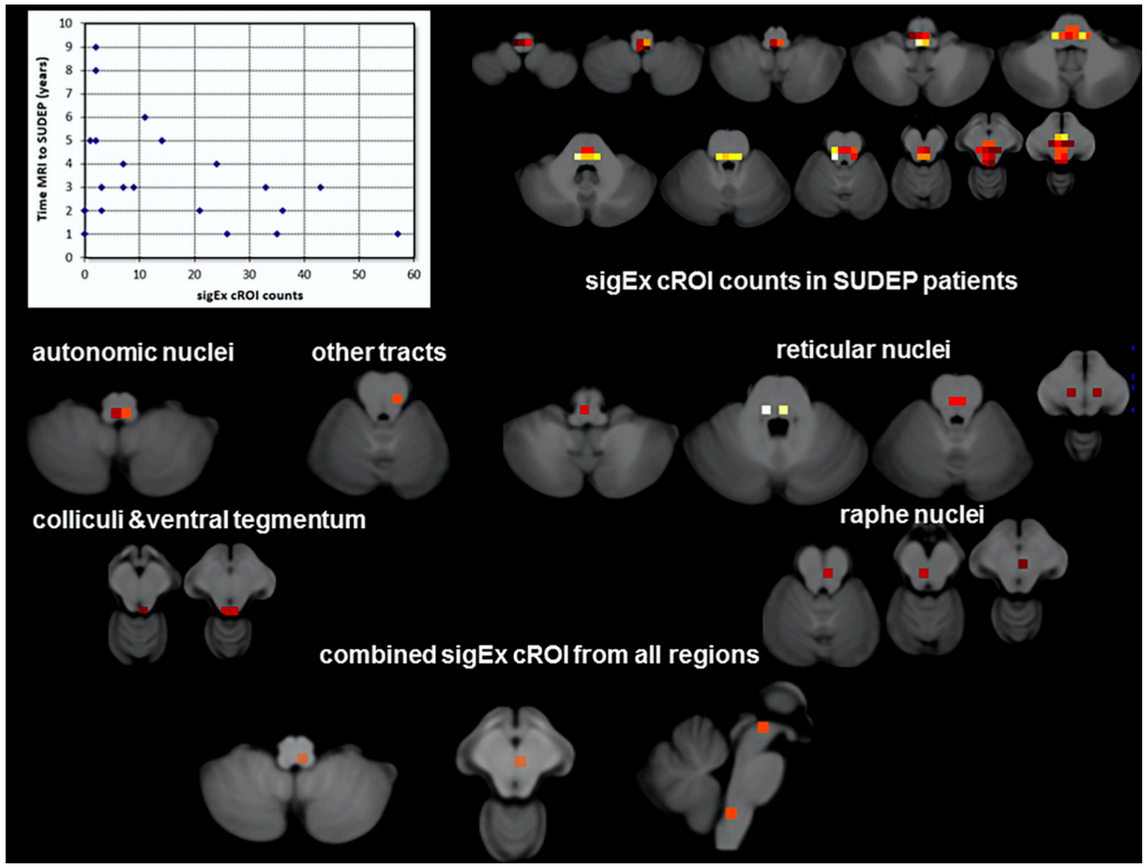


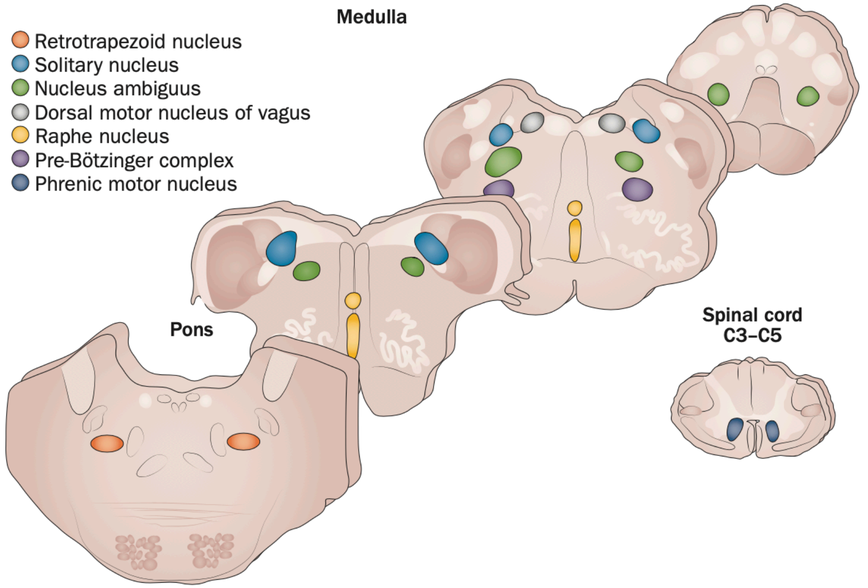
Brainstem network disruption: A pathway to sudden unexplained death in epilepsy?

Susanne G. Mueller[1] | Maromi Nei[2] | Lisa M. Bateman[3] | Robert Knowlton[4] | Kenneth D. Laxer[5] | Daniel Friedman[6] | Orrin Devinsky[6] | Alica M. Goldman[7]

Hum Brain Mapp *2018*: 39:

26 SUDEP, 18 focal epilepsy, 11 controls





- Volume loss in these regions correlates w/ autonomic dysfunction (HRV)
- Severity of volume loss ⇔ time to SUDEP

✓ Focal epilepsy ⇔ mesencephalic damage

✓ ↑ risk of SUDEP if expands into the medulla oblongata and nuclei involved in autonomic

Mueller et al. *Hum Brain Mapp* 2018

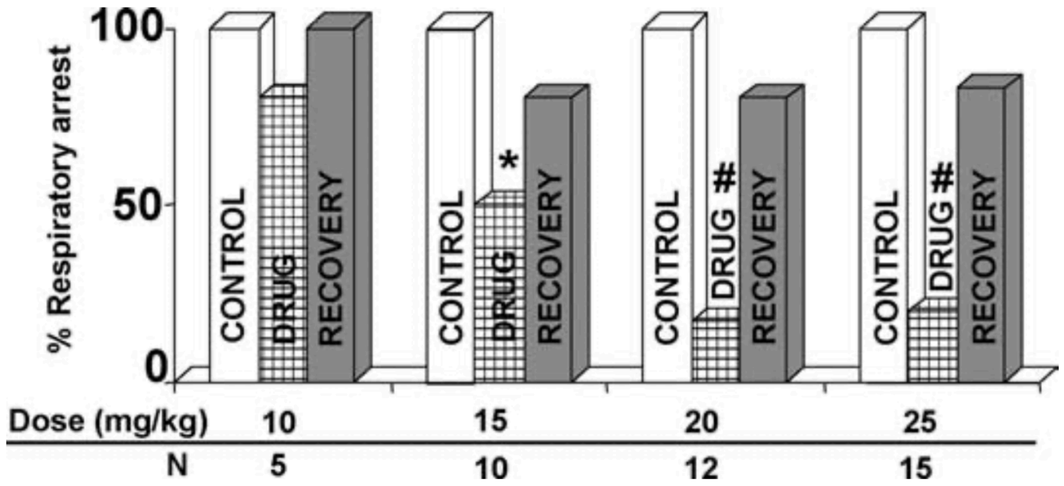
Evidence Supporting a Role of Serotonin in Modulation of Sudden Death Induced by Seizures in DBA/2 Mice

Srinivasan Tupal and Carl L. Faingold

Department of Pharmacology, Southern Illinois University School of Medicine, Springfield, Illinois, U.S.A.

Epilepsia, **47**(1):21–26, 2006

- DBA/2 mice: respiratory arrest(RA) after audiogenic seizure(AGS)
- Fluoxetine reduced incidence of RA



Epilepsia, 51(3):465–468, 2010
doi: 10.1111/j.1528-1167.2009.02248.x

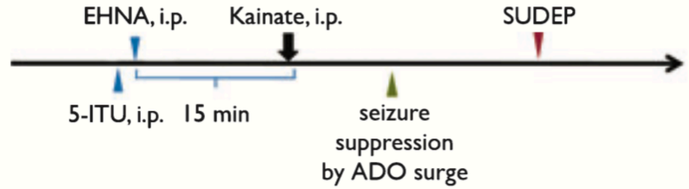
BRIEF COMMUNICATION

A novel mouse model for sudden unexpected death in epilepsy (SUDEP): Role of impaired adenosine clearance

Hai-Ying Shen, Tianfu Li, and Detlev Boison

Robert Stone Dow Neurobiology Laboratories, Legacy Research, Portland, Oregon, U.S.A.

A *EHNA/ITU: inhibition of adenosine-removing enzyme*



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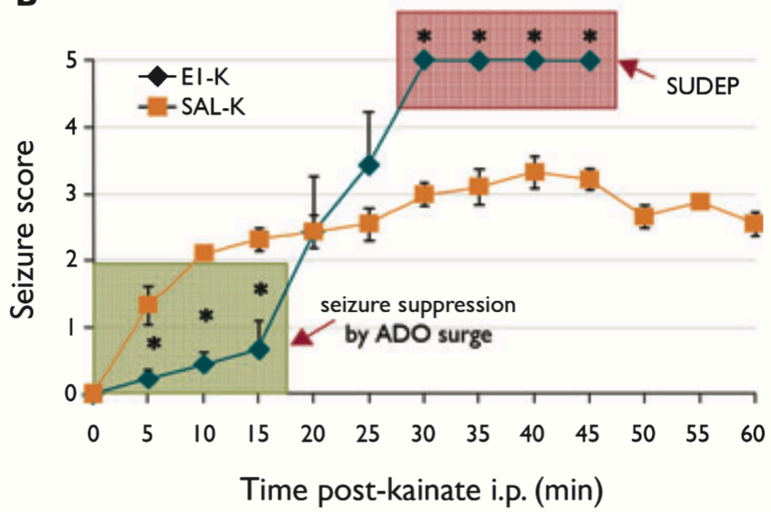
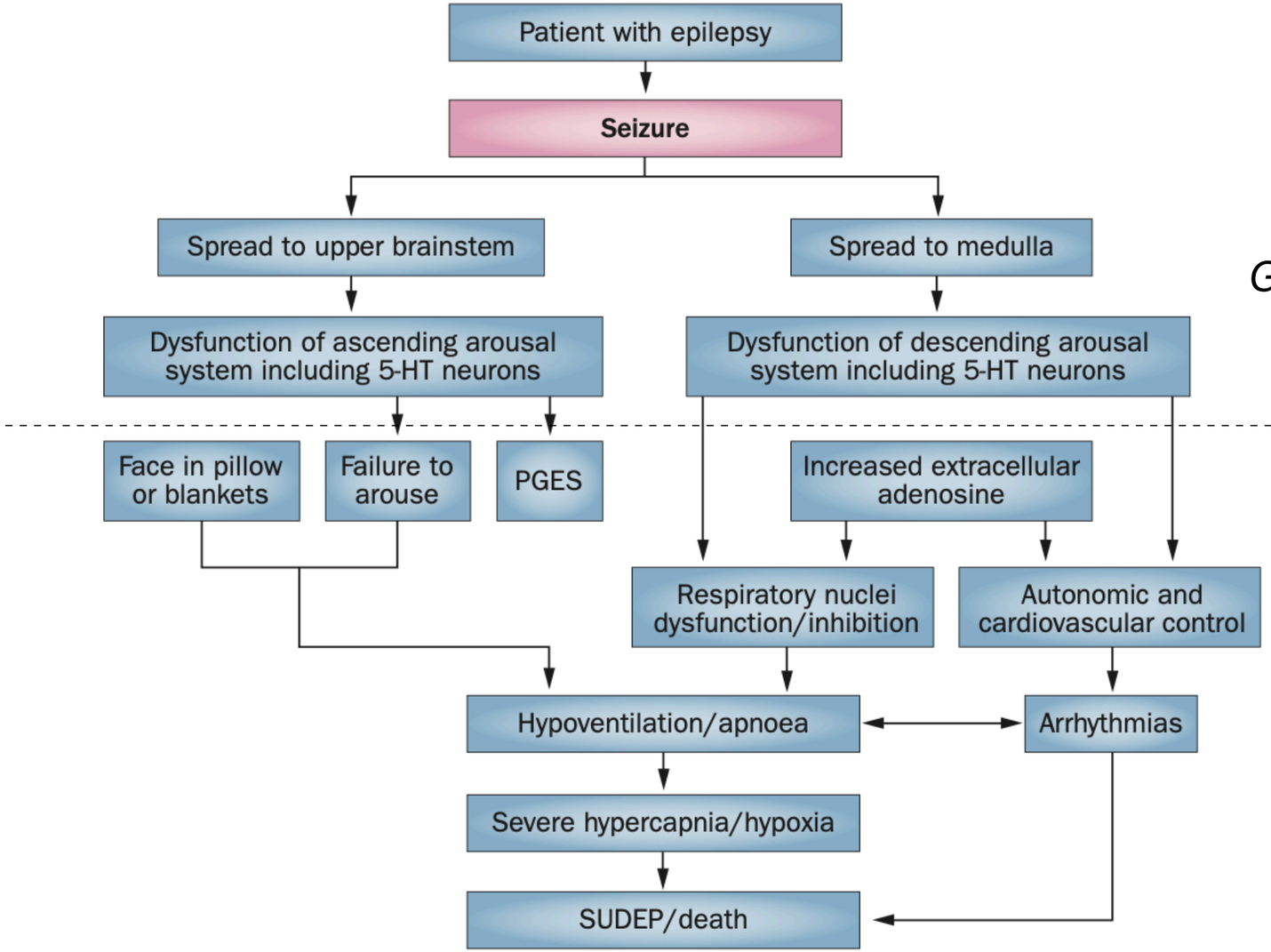


Serotonin : stimulation of breathing & arousal; defect in 5-HT system -> ↑ susceptibility of SUDEP

SUDEP is a consequence of an overactivation of adenosine receptor, opiate receptor

Tupal & Faingold. *Epilepsia* 2006; Shen et al. *Epilepsia* 2010

NO single mechanism established



Generalized suppression of brain activity

Suppression of brain stem functions

Postictal stage

Postictal brainstem dysfunction

A. Arousal
B. Respiratory
C. Cardiac

Genetic factors?

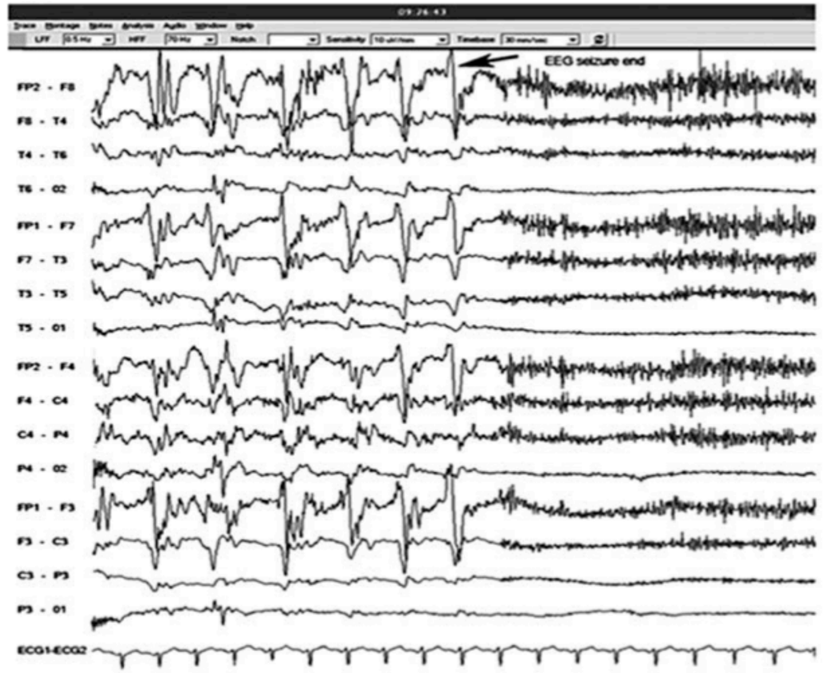
modified from Massey et al. *Nat Rev Neurol* 2014

Potential Biomarkers for SUDEP

An Electroclinical Case-Control Study of Sudden Unexpected Death in Epilepsy

Duration, s	Unadjusted			Adjusted[b]		
	Odds Ratio	95% CI	*p*	Odds Ratio	95% CI	*p*
>10	1.49	0.42–5.29	0.54	1.62	0.44–5.95	0.47
>20	1.64	0.47–5.78	0.44	1.84	0.52–6.54	0.34
>30	2.05	0.59–7.13	0.26	2.11	0.63–7.05	0.22
>40	2.94	0.82–10.6	0.10	3.0	0.87–10.41	0.082
>50	5.25	1.28–22.64	<0.05	5.22	1.26–21.58	<0.05
>60	9.49	1.58–56.14	<0.05	10.06	1.52–66.54	<0.05
>70	9.49	1.58–56.14	<0.05	10.06	1.52–66.54	<0.05
>80	19.29	2.91–128.02	<0.005	23.46	2.92–188.54	<0.005
>90	19.29	2.91–128.02	<0.005	23.46	2.92–188.54	<0.005

<10 mV, >1 sec, within 30 sec of sz cessation
40-60% of those who had GTCS (1-2% of focal sz)



- Posti-ctal generalized EEG suppression(PGES): longer in generalized motor seizure
- Prolonged PGES (>50s) appears to identify DRE who are at risk
- **But not all studies!!!** (Surges, 2011) -> "*Conflicting evidence regarding relation with SUDEP*"

Lhatoo et al. *Ann Neurol* 2010

Potential Biomarkers for SUDEP

Genetic

- Genetic epilepsies with increased SUDEP risk
- Cardiac arrhythmia genes (7-15%)
- Respiratory genes

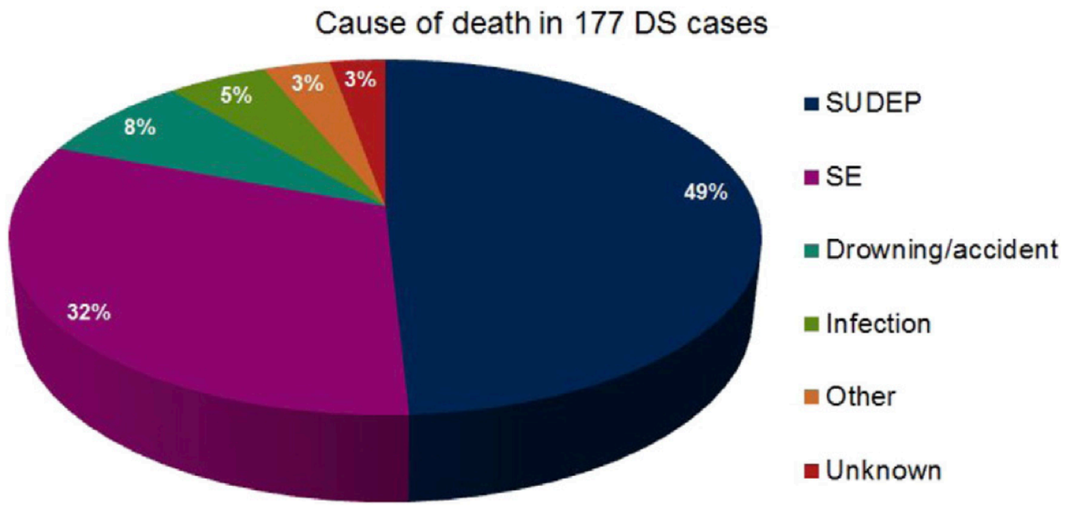


Table 1 | Selected gene mutations that increase the risk of SUDEP

Gene	Protein	Associated human disease	Human disease manifestations	Mouse model phenotype	SUDEP	Reference
SCN1A	$Na_v1.1$	Dravet syndrome	Febrile seizures in children; refractory seizures in adults; psychomotor regression; ataxia; sleep disturbance; cognitive impairment; premature death	Interictal heart rate variability; atropine-sensitive ictal bradycardia; premature death	Yes	Kalume (2013)[80] Kalume *et al.* (2013)[88] Auerbach *et al.* (2013)[127]
*SCN5A**	$Na_v1.5$	Brugada syndrome	ST-segment elevation in V1–V3 on electrocardiogram; syncope; seizure; disrupted sleep; premature death	Ventricular tachycardia; cardiac abnormalities	Possibly	Hedley *et al.* (2009)[128] Martin *et al.* (2012)[129] Derangeon *et al.* (2012)[130]
SCN5A‡	$Na_v1.5$	Long QT syndrome type 3	Delayed repolarization; torsades de pointes; sudden death; palpitations; syncope; gastrointestinal symptoms	QT prolongation, ventricular tachycardia and early afterdepolarization *in vitro*	Possibly	Aurlien *et al.* (2009)[131] Johnson *et al.* (2009)[132]
KCNA1	$K_v1.1$	NA	Episodes of ataxia with continuous inter-attack myokymia; partial epilepsy in some cases	Severe epilepsy; atrioventricular conduction block; bradycardia; premature ventricular contractions; premature death	Yes	Glasscock *et al.* (2010)[79] Zuberi *et al.* (1999)[133]
KCNH2	$K_v11.1$	Long QT syndrome type 2	Delayed repolarization of the heart; torsades de pointes; heart palpitations; syncope; sudden death; long QT events triggered by auditory stimuli	*Kcnh2*$^{-/-}$ genotype is embryonic lethal	Yes	Anderson *et al.* (2014)[74] Johnson *et al.* (2009)[132] Tu *et al.* (2011)[134]
KCNQ1	$K_v7.1$	Long QT syndrome type 1	Delayed repolarization of the heart; torsades de pointes; palpitations; syncope; sudden death; hearing loss; long QT events during swimming	Impaired neuronal repolarization; seizures; dysregulated autonomic control of heart	Yes	Goldenberg & Moss (2008)[71] Goldman *et al.* (2009)[77]
HTR2C	5-HT_{2c}	NA	NA	Epilepsy; respiratory arrest; cardiac monitoring not completed	Yes	Tecott *et al.* (1995)[23]
RYR2	RyR2	Catecholaminergic polymorphic ventricular tachycardia	Tachycardia due to catecholamine release during exercise; dizziness; syncope; seizures; premature death	Exercise-induced ventricular arrhythmias; generalized tonic–clonic seizures; sudden cardiac death	Yes	Derangeon *et al.* (2012)[129] Lehnart *et al.* (2008)[135] Napolitano *et al.* (1993)[136]

*Loss-of-function mutation. ‡Gain-of-function mutation. Abbreviations: NA, not applicable; SUDEP, sudden unexpected death in epilepsy.

Shmuely et al. *Epilepsy Behav* 2016; Massey CA et al. *Nat Rev Neurol* 2014

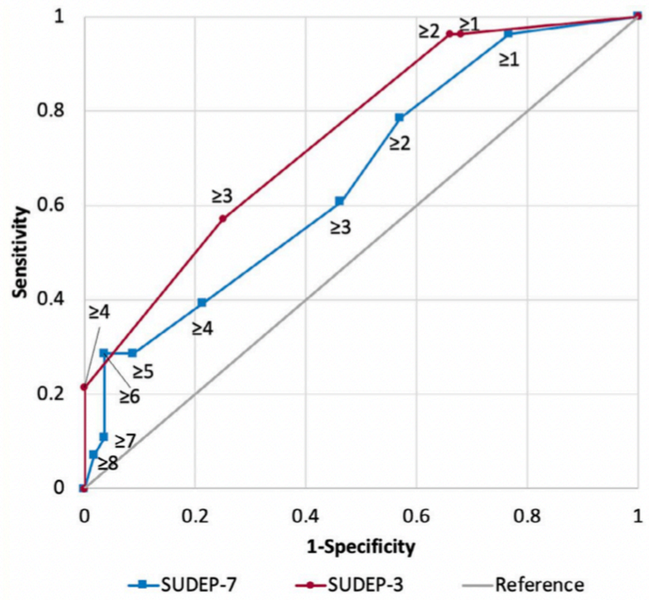
Identifying Patients at Risk

SUDEP inventory

SUDEP-7 → revised SUDEP-7 → SUDEP-3

2010 2015 2021

Risk factor	Odds ratio	SUDEP-7	Revised SUDEP-7
GCTS in the past 12 months		0 seizures → 0 points	0 seizures → 0 points
	2.4	1-3 seizures → 1 point	1-3 seizures → 1 point
	8.1	≥4 seizures → 3 points	≥4 seizures → 2 points
Any seizure, frequency per month in the past 12 months		0 seizures → 0 points	0 seizures → 0 points
	2.2, 3.8, 4.6[a]	1-49 seizures → 1 point	1-49 seizures → 1 point
	11.5	>50 seizures → 3 points	>50 seizures → 2 points
Epilepsy duration		0-29 y → 0 points	
	13.9	≥30 y → 3 points	
Number of AEDs		0-2 drugs → 0 points	
	4.0	≥3 drugs → 1 point	
Cognitive impairment		IQ ≥ 70 → 0 points	
	5.0	IQ < 70 → 2 points	
Total score		12 points	10 points



SUDEP risk factors	SUDEP–3 weighting	OR (95% CI)
GTC seizure frequency >3 in last year	0 or 1	2.7 (0.9-7.7)
Seizure of any type >0 in last year	0 or 2	8.4 (1.0-71.1)
Intellectual disability	0 or 1	3.1 (0.7-13.4)
Total SUDEP-3 score	0 to 4	

Obstructive Sleep Apnea is a Risk Factor for Sudden Unexplained Death in Epilepsy (SUDEP)

Atiwat Soontornpun, MD[1,2]; Noah D Andrews, RPSGT[1]; James Bena, MS[3]; Madeleine M Grigg-Damberger, MD[4]; Nancy Foldvary-Schaefer, DO, MS[1]

[1]Department of Neurology, Sleep Disorders and Epilepsy Centers, Cleveland Clinic, Cleveland, OH, USA; [2]Department of Internal Medicine, Chiang Mai University, Chiang Mai, Thailand; [3]Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA; [4]Department of Neurology, University of New Mexico, New Mexico, USA

Background

- OSA is at least 2-fold as common in adults with epilepsy (AWE).
- SUDEP is second only to stroke in potential years of life lost to neurologic diseases in U.S.
- Most cases of SUDEP occur during sleep and are associated with terminal apnea.
- **AIM OF STUDY**: Evaluate association between PSG-confirmed OSA and SUDEP risk in AWE using revised SUDEP Risk Inventory (rSUDEP-7).

Methods

- Retrospective observational study using Cleveland Clinic database of AWE who had PSG from Jan 2004 to Dec 2016.
- Data collection:
  - Demographics & clinical characteristics including smoking status, SSRI/SNRI use
  - Epilepsy characteristics: classification, duration, nocturnal seizures/drug-resistant epilepsy(DRE), seizure frequency, number of antiseizure medications(ASMs), ASM standardized dose
  - rSUDEP-7
  - Sleep variables: AHI, SpO2 nadir, TST <90%, ODI 3%, Epworth Sleepiness Scale(ESS) score
- Statistical analysis
  - Association between rSUDEP-7 and OSA groups using Wilcoxon rank sum tests
  - Relationships between rSUDEP-7and AHI/ODI using Spearman correlation
  - Multivariable linear models adjusted for age, gender, BMI and smoking status

Results

- A total of 214 participants were included. Mean age was 43 y, and 57% were female.
- 134 (62%) of the cohort had OSA.

Table 1 Demographic and clinical characteristics of patients

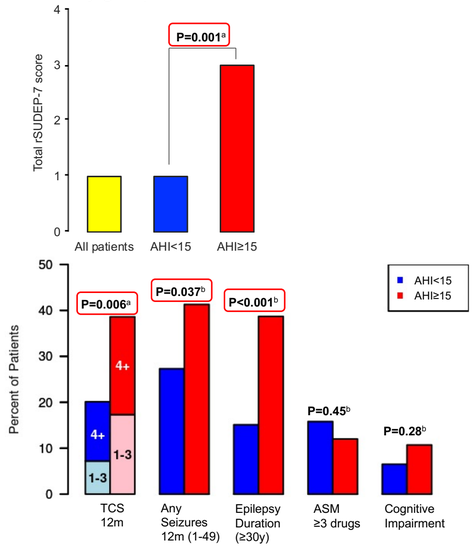
	Total (n=214)	AHI <15 (n=139)	AHI ≥15 (n=75)	p-value
Age, y	43.5 ± 14.4	40.6 ± 14.4	48.9 ± 13.0	**<0.001**[a]
Race, Caucasian	179 (83.6)	121 (87.1)	58 (77.3)	**0.022**[b]
BMI, kg/m^2	31.3 ± 7.9	29.9 ± 7.2	33.9 ± 8.4	**<0.001**[a]
Neck circumference, cm	39.1 ± 4.8	38.7 ± 4.8	39.8 ± 4.6	0.11[a]
Active Smoker	49 (22.9)	33 (23.7)	16 (21.3)	0.69[c]
Cognitive Impairment	17 (7.9)	9 (6.5)	8 (10.7)	0.28[c]
SSRI/SNRI use	63 (29.4)	40 (28.8)	23 (30.7)	0.77[c]
Focal-onset epilepsy	157 (73.4)	100 (71.9)	57 (76.0)	0.44[d]
Nocturnal seizures	63 (29.4)	33 (23.7)	30 (40.0)	**0.013**[c]
Drug-resistant epilepsy	72 (33.6)	39 (28.1)	33 (44.0)	**0.019**[c]
Epilepsy duration, y	18.0 [6.0, 29.0]	15.0 [6.0, 25.0]	25.0 [11.0, 39.0]	**0.001**[d]
Seizure frequency, per mo	0.0 [0.0, 1.5]	0.0 [0.0, 1.0]	0.1 [0.0, 2.0]	0.33[d]
ASM standardized dose	1.6 [1.0, 2.7]	1.7 [1.0, 3.1]	1.3 [1.0, 2.3]	0.15[d]
ESS	8.4 ± 4.7	8.3 ± 4.7	8.7 ± 4.8	0.55[a]
AHI	8.9 [1.5, 21.1]	2.6 [0.7, 8.8]	28.2 [19.4, 45.3]	n/a
TST <90%, %	0.5 [0.0, 5.6]	0.2 [0.0, 3.0]	2.4 [0.3, 9.7]	**<0.001**[d]
SpO_2 nadir, %	87.0 [83.0, 91.0]	89.0 [86.0, 92.0]	85.0 [79.0, 88.0]	**<0.001**[d]
SpO_2 <90%, %	0.5 [0.0, 5.6]	0.20 [0.0, 3.0]	2.4 [0.3, 9.7]	**<0.001**[d]
ODI 3%*	3.6 [0.5, 12.4]	1.3 [0.2, 4.3]	14.5 [7.2, 29.3]	**<0.001**[d]

Statistics presented as Mean ± SD, Median [P25,P75], n(%); p-values: a=t-test, b=Fisher's Exact test, c=Pearson's chi-square test, d=Wilcoxon rank sum test
*Data not available for all subjects. Missing values: ODI 3%=31

Table 2 Revised SUDEP Risk Inventory (rSUDEP-7)

Risk factor	rSUDEP-7
Tonic-clonic seizures (TCS), past 12 mo	0 seizures ⟶ 0 points 1-3 seizures ⟶ 1 point ≥4 seizures ⟶ 2 points
Seizure frequency, per mo past 12 mo	0 seizures ⟶ 0 points 1-49 seizures ⟶ 1 point ≥50 seizures ⟶ 2 points
Epilepsy duration	0-29 y ⟶ 0 points ≥30 y ⟶ 3 point
Number of ASMs	0-2 drugs ⟶ 0 points ≥3 drugs ⟶ 1 point
Cognitive impairment	absence ⟶ 0 points presence ⟶ 1 point
Total score	**10 points** (the higher the score, the greater risk of SUDEP)

Figure 1 Comparisons of rSUDEP-7 scores & items by OSA severity groups

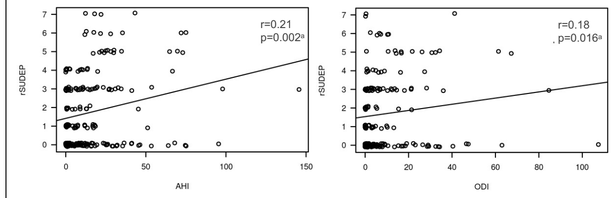


p-values: a=Wilcoxon rank sum test, b= Pearson's chi-square test

Results (cont.)

- Those with moderate-to-severe OSA had higher rSUDEP-7 scores than those with AHI <15 (3 points vs 1 point).
- After adjusting for age, sex, BMI, and smoking status, those with AHI ≥15 had mean rSUDEP-7 score **1.14 points higher** than those with AHI <15.

Figure 2 Association between rSUDEP-7 and PSG and Clinical variables



- Higher AI and ODI were positively correlated with rSUDEP-7 scores.
- No significance for age[a], race[b], gender[b], BMI[a], smoking[b], use of SSRI/SNRI[b], epilepsy type[b], ESS[a]

p-values: a=Spearman's correlation, b=Kruskal-Willis test

Conclusions

- AWE and moderate-to-severe OSA have higher risk of SUDEP using rSUDEP-7.
- AWE and OSA have higher seizure frequency including GTCS and nocturnal seizures.
- These findings suggest OSA may participate in the pathophysiology of SUDEP and provide further support for routine screening of OSA in AWE

Cochrane Library

Cochrane Database of Systematic Reviews

Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP) (Review)

Maguire MJ, Jackson CF, Marson AG, Nevitt SJ

We included one cohort study and three case-control studies of serious to critical risk of bias. The 6-month prospective cohort study observed no significant effect of providing patients with SUDEP information on drug compliance and quality of life, anxiety and depression levels. The study was too short and with no deaths observed in either group to determine a protective effect. Two case control studies reported a protective effect for nocturnal supervision against SUDEP. However due to significant heterogeneity, the results could not be combined in meta-analysis. One study of 154 SUDEP cases and 616 controls reported an unadjusted odds ratio (OR) of 0.34 (95% CI 0.22 to 0.53; P < 0.0001). The same study demonstrated the protective effect was independent of seizure control, suggesting that nocturnal supervision is not just a surrogate marker of seizure control. The second case-control study of 48 SUDEP cases and 220 controls reported

Authors' conclusions

We found limited, very low-certainty evidence that supervision at night reduces the incidence of SUDEP. Further research is required to identify the effectiveness of other current interventions — for example seizure detection devices, safety pillows, SSRIs, early surgical evaluation, educational programmes, and opiate and adenosine antagonists — in preventing SUDEP in people with epilepsy.

Plan for SUDEP Risk Reduction

Active & effective epilepsy management

1. Seizure reduction, particularly GTCS reduction
2. Treatment adherence, avoid triggers for seizures
3. Educating care plans for seizure clusters & home management
4. Consider other treatments when ASMs are not sufficient to control seizures
5. Use of noctural supervision/listening device when feasible (cultural acceptance)

If witnessed, turning patient to recovery position & stimulating the patient may help

Basic life supports training to willing caregivers of high-risk patients

Talking about SUDEP

2008 AES Task Force report

- “The potentially increased risk of death associated with epilepsy should be disclosed in the context of a comprehensive education program”

2012 Institute of Medicine Report

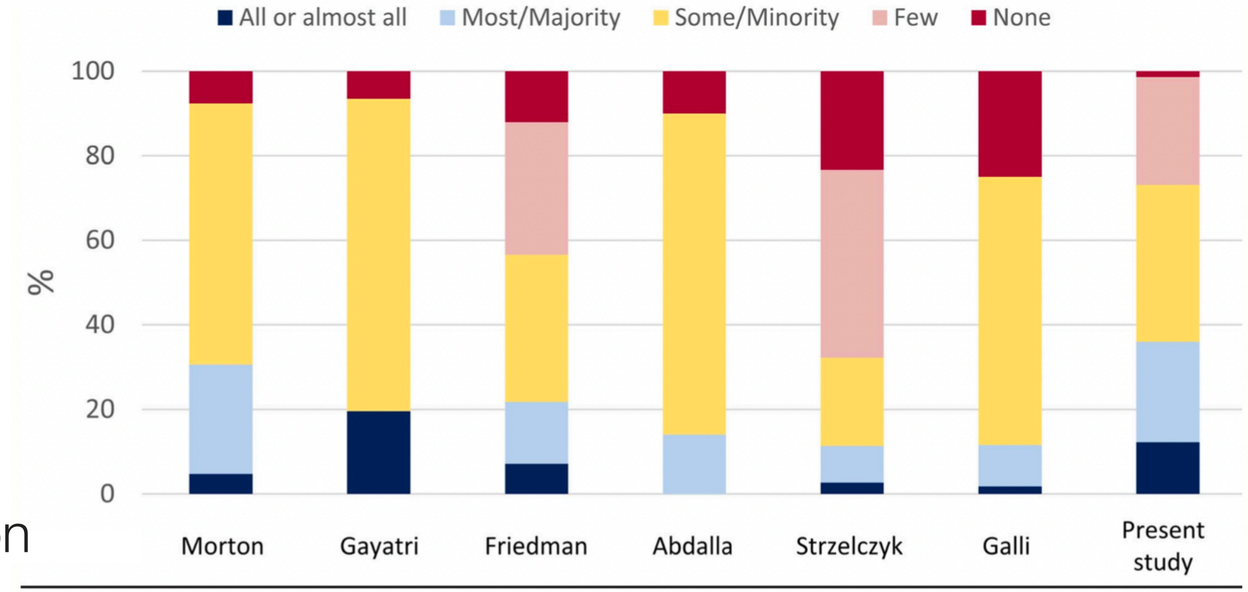
- “To manage fears and prevent unnescessary anxiety, PWE and their families need complete and accurate information about the comorbidities and mortality risks associated with epilepsy, SUDEP”

2017 AAN/AES Recommendations

- “Inform PWE and parents of children with epilepsy of the risk” “Inform PWE that seizure freedom, particularly freedom from GTCS, is strongly associated with a decreased risk of SUDEP”

Talking about SUDEP

- Only 18% recalled SUDEP discussion - of those that didn't[1]:
  - *72% of families wished it was discussed*, 17% were unsure
- Preference for SUDEP information around time of diagnosis, from neurologists[2]
- Ethical considerations
  - ☑ Consistent with principles of autonomy
  - ☑ Truth telling is preserved
  - ☑ Allows for natural psychological adaptation



	Morton	Gayatri	Friedman	Abdalla	Strzelczyk	Galli	Present study
Year of survey	≤2005*	≤2009*	2011	≤2013*	2014	2015	2017/18
Country	UK	UK	USA and Canada	Brazil	Austria, Germany, Switzerland	Italy	Mainly USA
N	383	46	1101	44	519	112	369

1. Louik et al *Epilepsy Behav* 2017; 2. Ramanchandran Nair et al. *Epilepsy Behav* 2016; 3. Keller et al. *Epilepsia Open* 2020

Conclusions

- Sudden unexpected death (SUDEP) is an important direct epilepsy-related cause
- Pediatric SUDEPs are more common than suspected
- The most significant risk factor is, but NOT limited to, frequent GTCS
- Multiple pathophysiologic may be involved, genetic factors may also play a role
- Awareness/education is the most accessible tool we have for SUDEP prevention
- SUDEP prevention remain a big challenge

ขอบคุณครับ

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