



# Updating SUDEP Mechanisms & Prevention

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# Disclosures

None relevant to this presentation

# Learning Objectives

- 1) Describe the definition of sudden unexpected death in epilepsy (SUDEP)
- 2) Identified established risk factors for SUDEP
- 3) Describe potential pathomechanisms that might promote SUDEP
- 4) Identify strategies to minimize the risk of SUDEP

# Mortality in Epilepsy

- Standardized Mortality Ratio (SMR): 2.2-2.6
- Etiologies of mortality:
  1. Deaths due to epilepsy:
    - ▶ direct consequence of seizure
    - ▶ **SUDEP**
  2. Deaths related to the cause of epilepsy
  3. Deaths unrelated to epilepsy
- Causes **2-17%** of all deaths in PWE

**Table 3** Standardized mortality ratios for sudden, unexplained death for patients age 20 to 40, 1960 to 1989

Parameter	Total patients	No. of males	No. of females
Number of SUDEP patients	5	1	4
SUDEP rate per 1,000	1.449	0.655	2.079
Expected rate per 1,000*	0.061	0.087	0.041
Expected no. of patients	0.212	0.133	0.079
SMR	<b>23.7</b>	7.5	50.7
95% CI	7.7-55.0	0.2-41.8	13.8-129.9

\* From Shen et al.<sup>28</sup>

Ficker et al. *Neurology* 1998

## 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
- ☑ **NOT** a consequence of trauma, drowning, or status epilepticus
  - May be **witness or unwitnessed** ; evidence of a preceding Sz 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

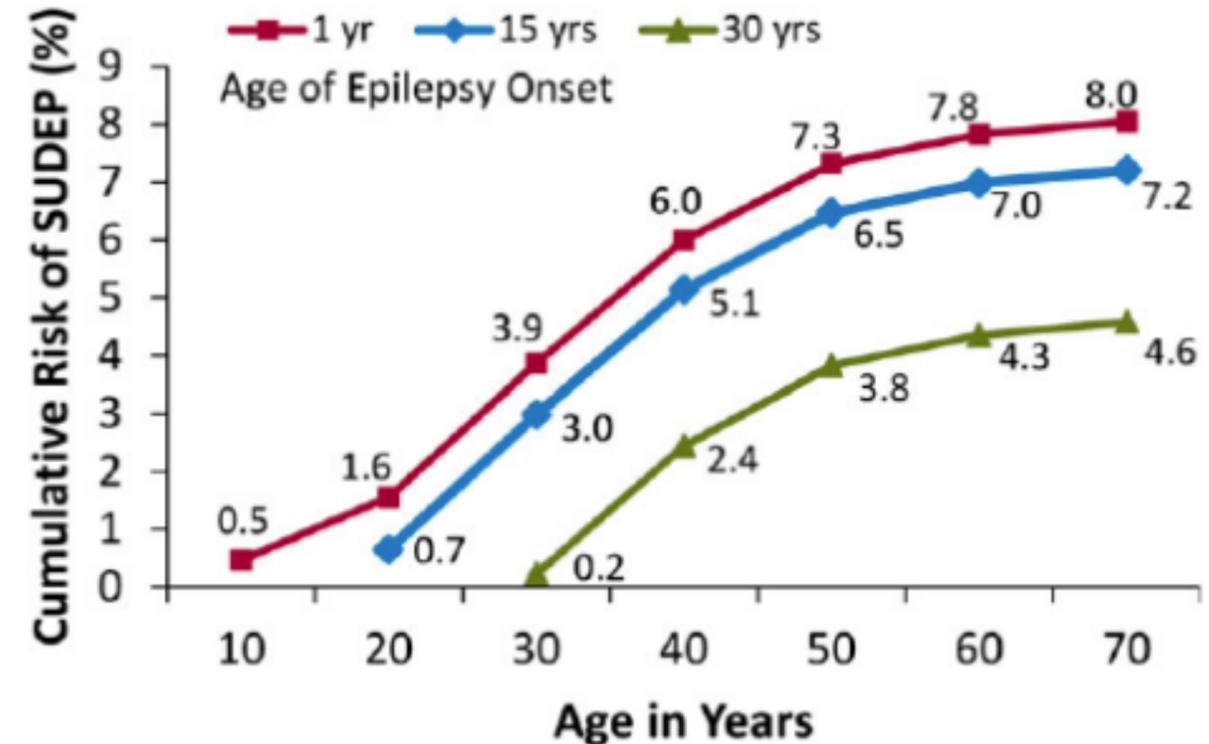
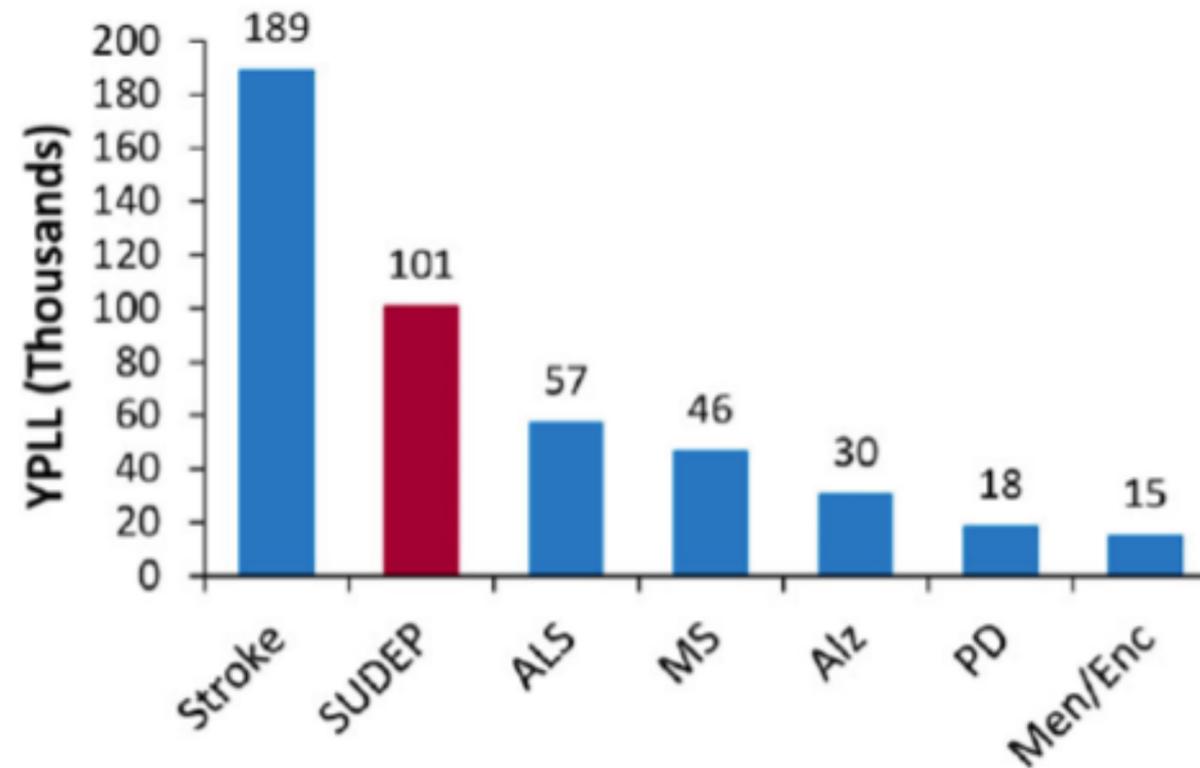
# Case Scenarios

- 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 exam. 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

# Sudden unexpected death in epilepsy: Assessing the public health burden

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

*Epilepsia*, 55(10):1479–1485, 2014



- ✓ 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



# 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

Neurology® 2017;88:1674-1680

**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

**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

## Incidence

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

# 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

*Neurology*<sup>®</sup> 2018;91:e107-e111. doi:10.1212/WNL.0000000000005762

✓ more common in children than widely 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
<b>Crude analysis</b>	All	17	0.27	1.17 (0.68–1.88)
	Definite, definite plus, probable	16	0.27	1.11 (0.63–1.79)
<b>Sensitivity analysis</b>	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)
<b>Capture-recapture analysis</b>	Definite, definite plus, probable	21	0.27	1.45 (0.90–2.22)
<b>From the literature</b>				
Source	Included classifications of SUDEP	Population		Incidence (95% CI) per 1,000 patient-years
<b>AAN guidelines<sup>1</sup></b>	Definite, definite plus, <sup>a</sup> probable	“Childhood”		0.22 (0.16–0.31)
	Definite, definite plus, <sup>a</sup> probable	“Adult”		1.22 (0.64–2.32)
<b>Sveinsson et al.<sup>2</sup></b>	Definite, definite plus, probable	<16 y		1.11 (0.45–2.29)
	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)

# 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

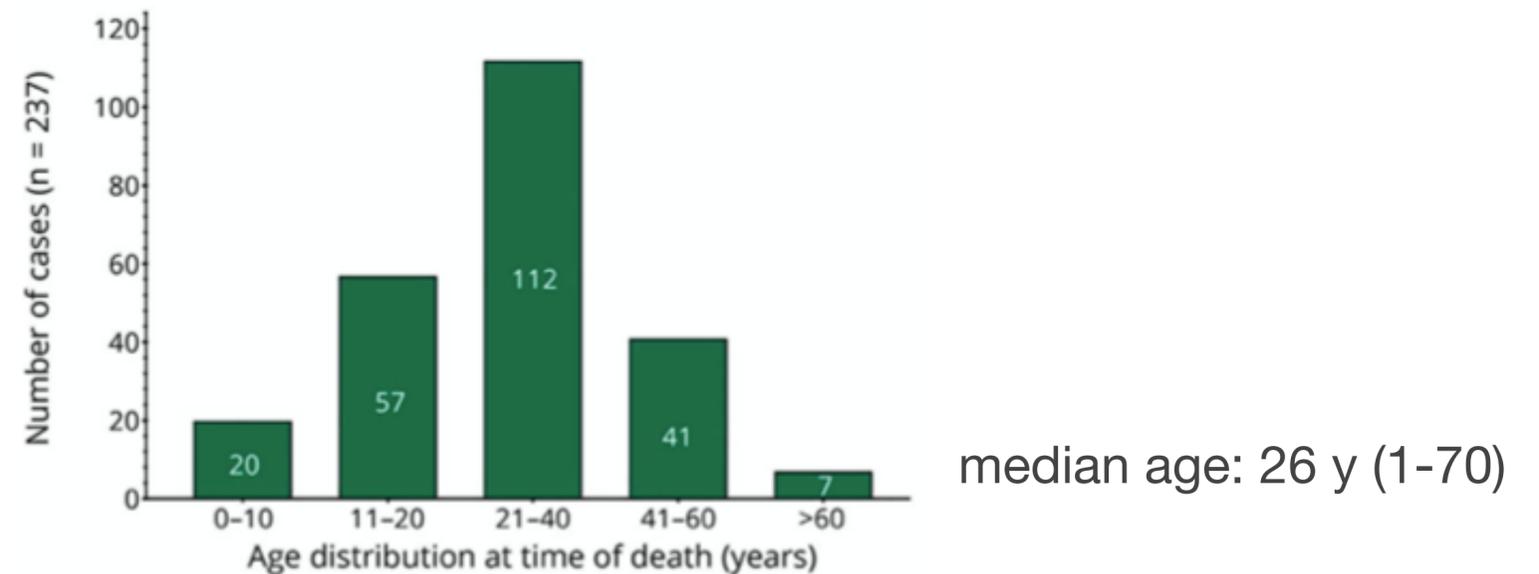
Neurology® 2019;93:e227-e236. doi:10.1212/WNL.00000000000007778

237 definite and probable SUDEP

✓ Young adult, during apparent sleep, were prone

**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



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

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Neurology® 2019;93:e227-e236. doi:10.1212/WNL.00000000000007778

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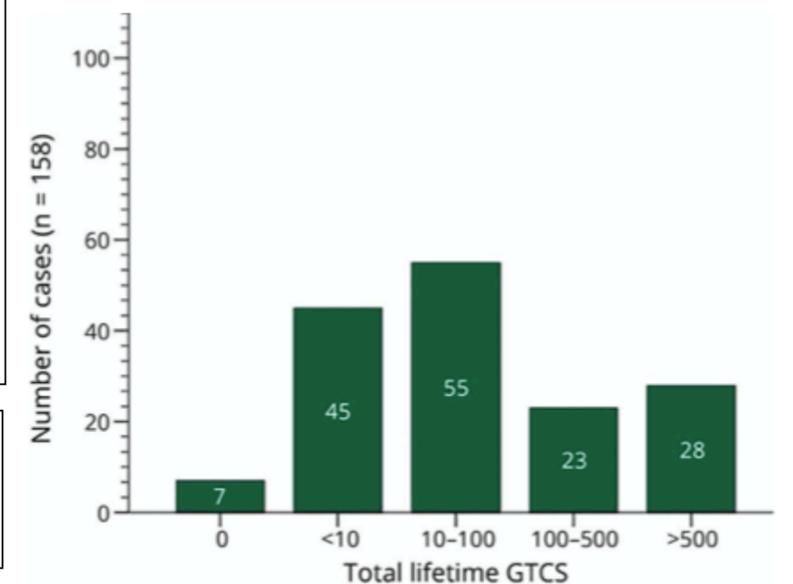
**Table 3** Seizure histories in cases of SUDEP with sufficient information to adjudicate (143 of 237)

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

- ✓ SUDEP affects the full spectrum of epilepsies
- ✓ GGE are also at risk
- ✓ SUDEP risk is **NOT** limited to frequent GTCS
- ✓ Should educate all PWE !!!

- 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%)



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- ✓ **GTCS**: *strongest* risk factor
- ✓ >3 GTCS /yr ↑ risk 15 times
- ✓ poor seizure control
- ✓ nocturnal supervision can ↓ risk

# Clinical risk factors in SUDEP

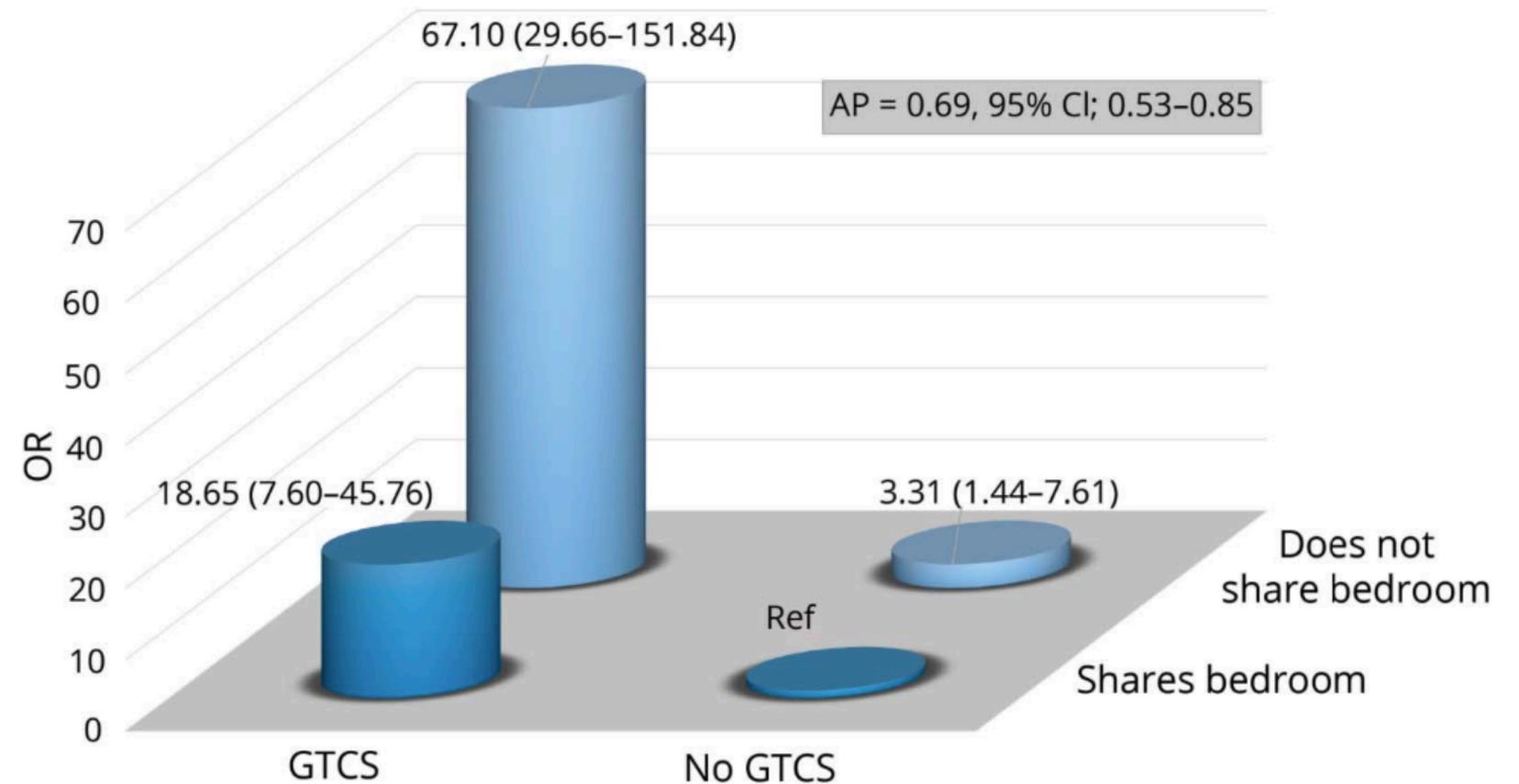
A nationwide population-based case-control study

Olafur Sveinsson, MD, MSc, Tomas Andersson, BSc, Peter Mattsson, MD, PhD, Sofia Carlsson, PhD, and Torbjörn Tomson, MD, PhD

*Neurology*® 2020;94:e419-e429.

- Sz during preceding year
  - *GTCS* 27x
  - nocturnal GTCS 15x
- Living alone 5x
- **NOT** sharing bedroom+GTCS **67x**

✓ GTCS who sleep alone have dramatically increased SUDEP risk



# Exome-Based Analysis of Cardiac Arrhythmia, Respiratory Control, and Epilepsy Genes in Sudden Unexpected Death in Epilepsy

Richard D. Bagnall,<sup>1,2</sup> Douglas E. Crompton,<sup>3,4</sup> Slavé Petrovski,<sup>4,5</sup> Lien Lam,<sup>1,2</sup> Carina Cutmore,<sup>1,2</sup> Sarah I. Garry,<sup>4</sup> Lynette G. Sadleir,<sup>6</sup> Leanne M. Dibbens,<sup>7</sup> Anita Cairns,<sup>8</sup> Sara Kivity,<sup>9</sup> Zaid Afawi,<sup>10</sup> Brigid M. Regan,<sup>4</sup> Johan Duflou,<sup>2,11</sup> Samuel F. Berkovic,<sup>4</sup> Ingrid E. Scheffer,<sup>4,12,13,14</sup> and Christopher Semsarian<sup>1,2,15</sup>

ANN NEUROL 2016;79:522–534

- 61 SUDEP cases
- Four SUDEP (7%) had mutations in common genes responsible for LQTS
- Nine SUDEP (15%) had candidate pathogenic variants in cardiac arrhythmia genes
- 25% epilepsy genes: DEPDC5 (6 cases)

**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 <sub>v</sub> 1.1	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) <sup>80</sup> Kalume <i>et al.</i> (2013) <sup>88</sup> Auerbach <i>et al.</i> (2013) <sup>127</sup>
SCN5A*	Na <sub>v</sub> 1.5	Brugada syndrome	ST-segment elevation in V1–V3 on electrocardiogram; syncope; seizure; disrupted sleep; premature death	Ventricular tachycardia; cardiac abnormalities	Possibly	Hedley <i>et al.</i> (2009) <sup>128</sup> Martin <i>et al.</i> (2012) <sup>129</sup> Derangeon <i>et al.</i> (2012) <sup>130</sup>
SCN5A†	Na <sub>v</sub> 1.5	Long QT syndrome type 3	Delayed repolarization; torsades de pointes; sudden death; palpitations; syncope; gastrointestinal symptoms	QT prolongation, ventricular tachycardia and early afterdepolarization <i>in vitro</i>	Possibly	Aurlien <i>et al.</i> (2009) <sup>131</sup> Johnson <i>et al.</i> (2009) <sup>132</sup>
KCNA1	K <sub>v</sub> 1.1	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 <i>et al.</i> (2010) <sup>79</sup> Zuberi <i>et al.</i> (1999) <sup>133</sup>
KCNH2	K <sub>v</sub> 11.1	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	<i>Kcnh2</i> <sup>-/-</sup> genotype is embryonic lethal	Yes	Anderson <i>et al.</i> (2014) <sup>74</sup> Johnson <i>et al.</i> (2009) <sup>132</sup> Tu <i>et al.</i> (2011) <sup>134</sup>
KCNQ1	K <sub>v</sub> 7.1	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) <sup>71</sup> Goldman <i>et al.</i> (2009) <sup>77</sup>
HTR2C	5-HT <sub>2c</sub>	NA	NA	Epilepsy; respiratory arrest; cardiac monitoring not completed	Yes	Tecott <i>et al.</i> (1995) <sup>23</sup>
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 <i>et al.</i> (2012) <sup>129</sup> Lehnart <i>et al.</i> (2008) <sup>135</sup> Napolitano <i>et al.</i> (1993) <sup>136</sup>

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

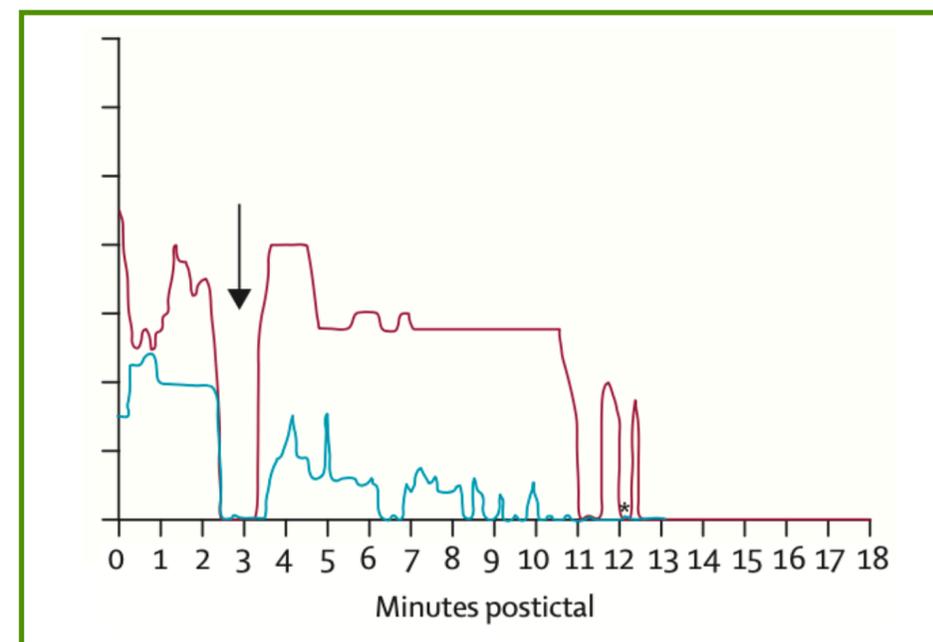
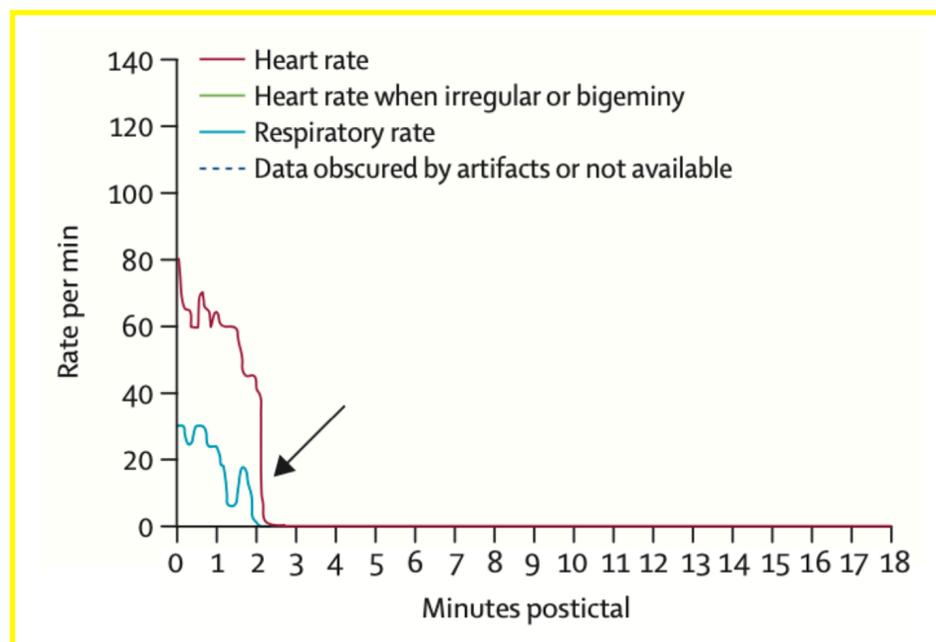
Genetic risk factors for SUDEP remain elusive

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

Lancet Neurol 2013; 12: 966-77

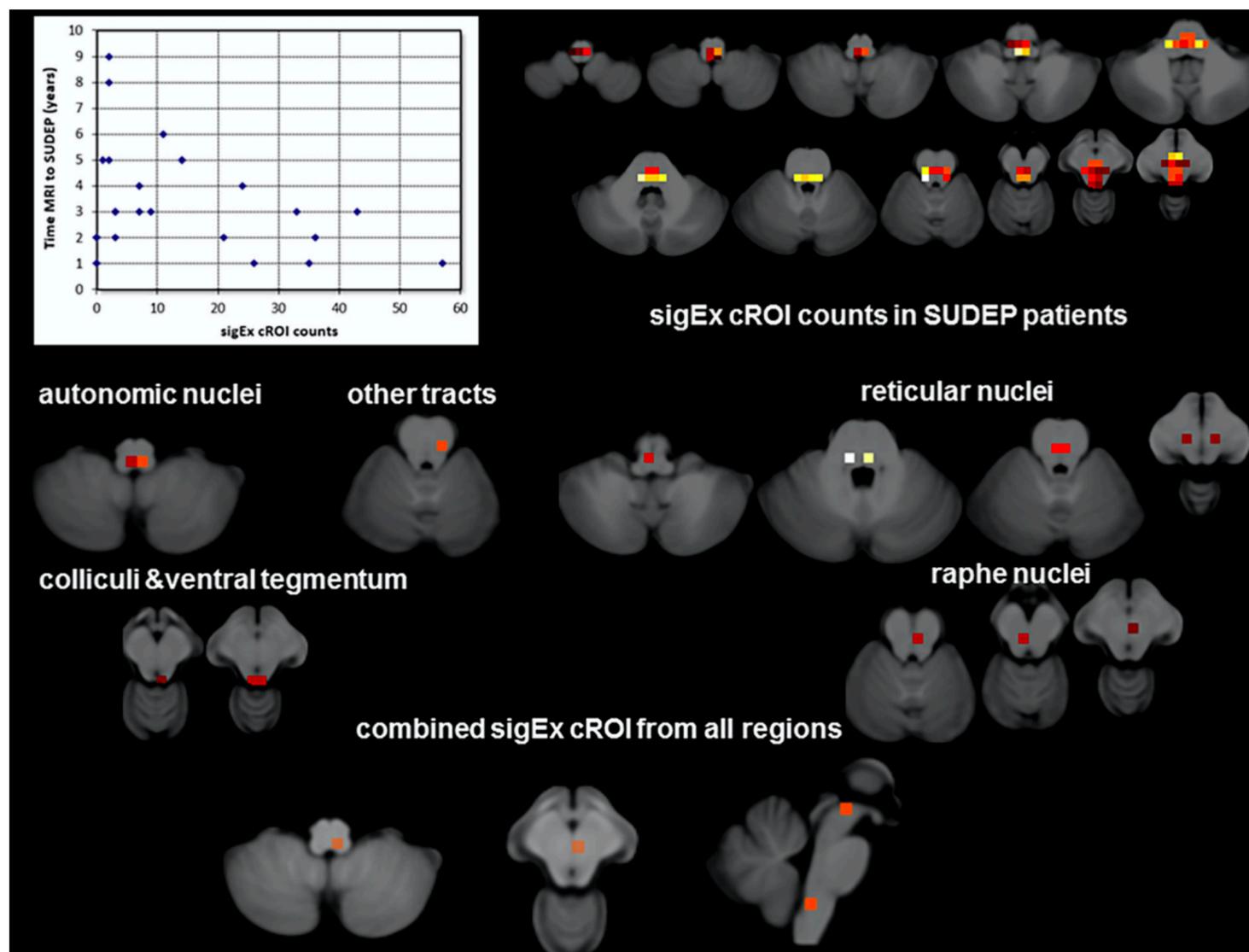
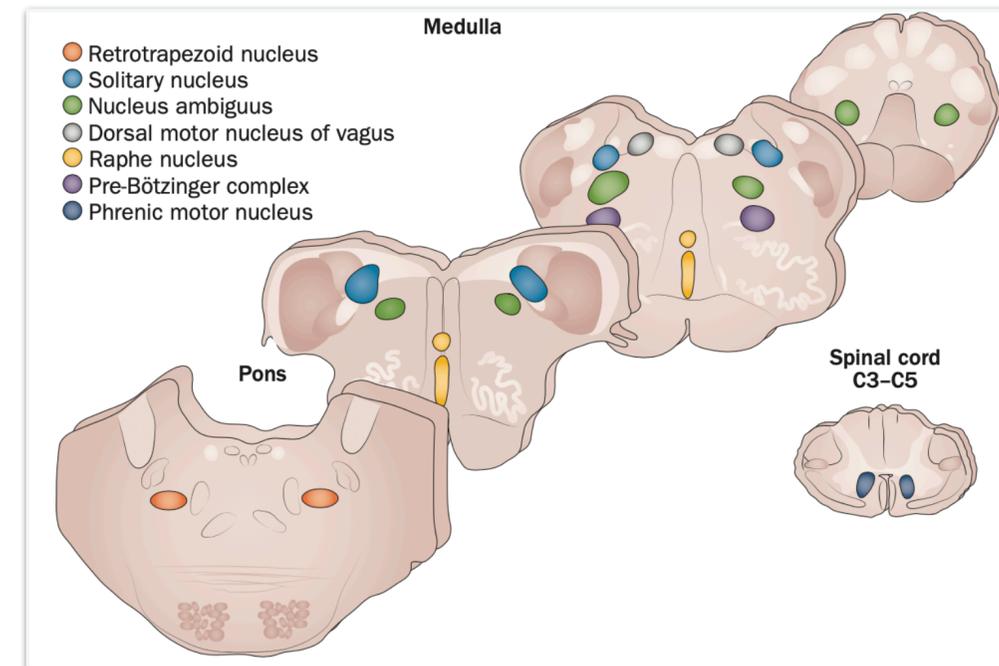
Philippe Ryvlin, Lina Nashef, Samden D Lhatoo, Lisa M Bateman, Jonathan Bird, Andrew Bleasel, Paul Boon, Arielle Crespel, Barbara A Dworetzky, Hans Høgenhaven, Holger Lerche, Louis Maillard, Michael P Malter, Cecile Marchal, Jagarlapudi M K Murthy, Michael Nitsche, Ekaterina Pataraiia, Terje Rabben,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

- 147 units; 16 SUDEP (11 monitored), 9 near-SUDEP
- Early postictal tachypnea → cardiorespiratory arrest w/n 3 min → reversed → terminal apnea/asystole
- *Time to CPR*: SUDEP 13-180 min; near-SUDEP  $\leq 3$  min



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

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



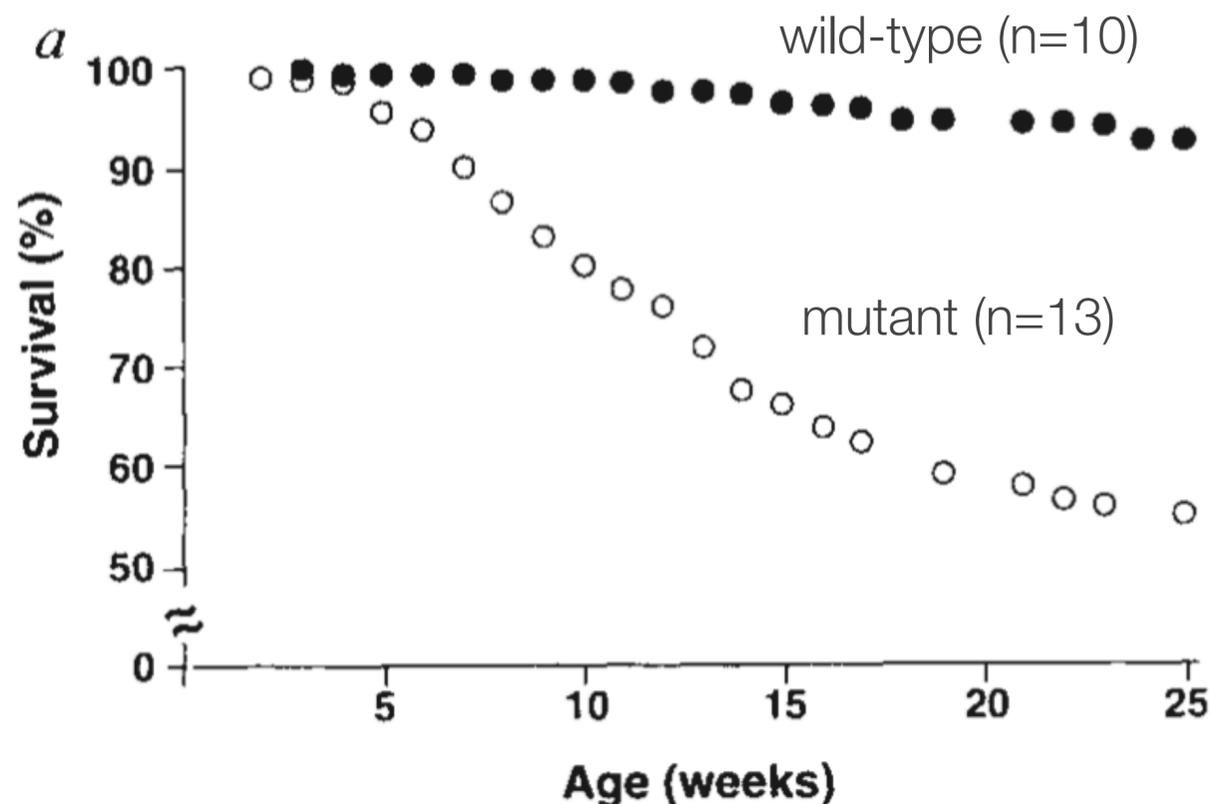
- Volume loss in these regions correlates w/ autonomic dysfunction (HRV)
- Severity of volume loss  $\Leftrightarrow$  time to SUDEP

- ✓ Focal epilepsy  $\Leftrightarrow$  mesencephalic damage
- ✓  $\uparrow$  risk of SUDEP if expands into the medulla oblongata and nuclei involved in autonomic

# Eating disorder and epilepsy in mice lacking 5-HT<sub>2C</sub> serotonin receptors

Laurence H. Tecott\*†, Linda M. Sun\*, Susan F. Akana‡, Alison M. Strack‡, Daniel H. Lowenstein§||, Mary F. Dallman‡ & David Julius\*¶

NATURE · VOL 374 · 6 APRIL 1995

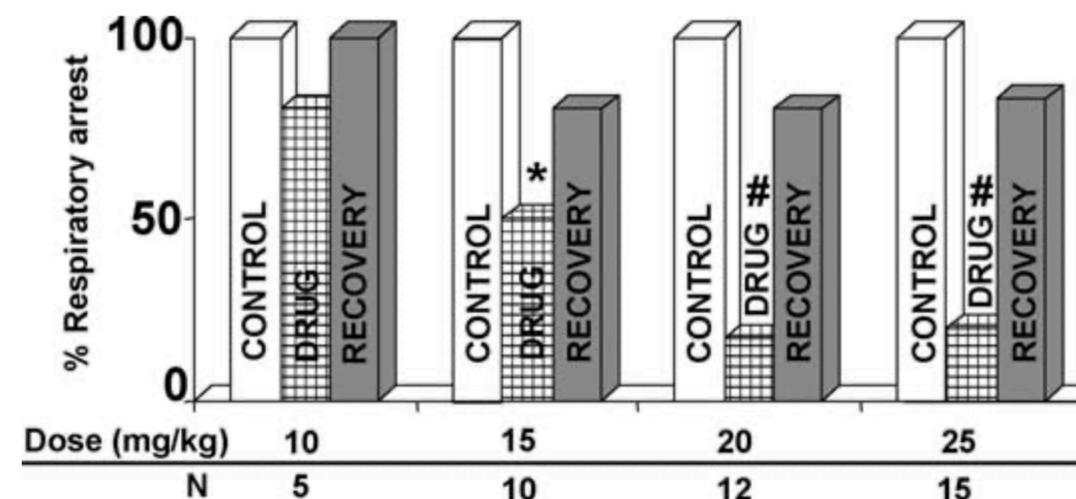


## Evidence Supporting a Role of Serotonin in Modulation of Sudden Death Induced by Seizures in DBA/2 Mice

Srinivasan Tupal and Carl L. Faingold

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

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



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

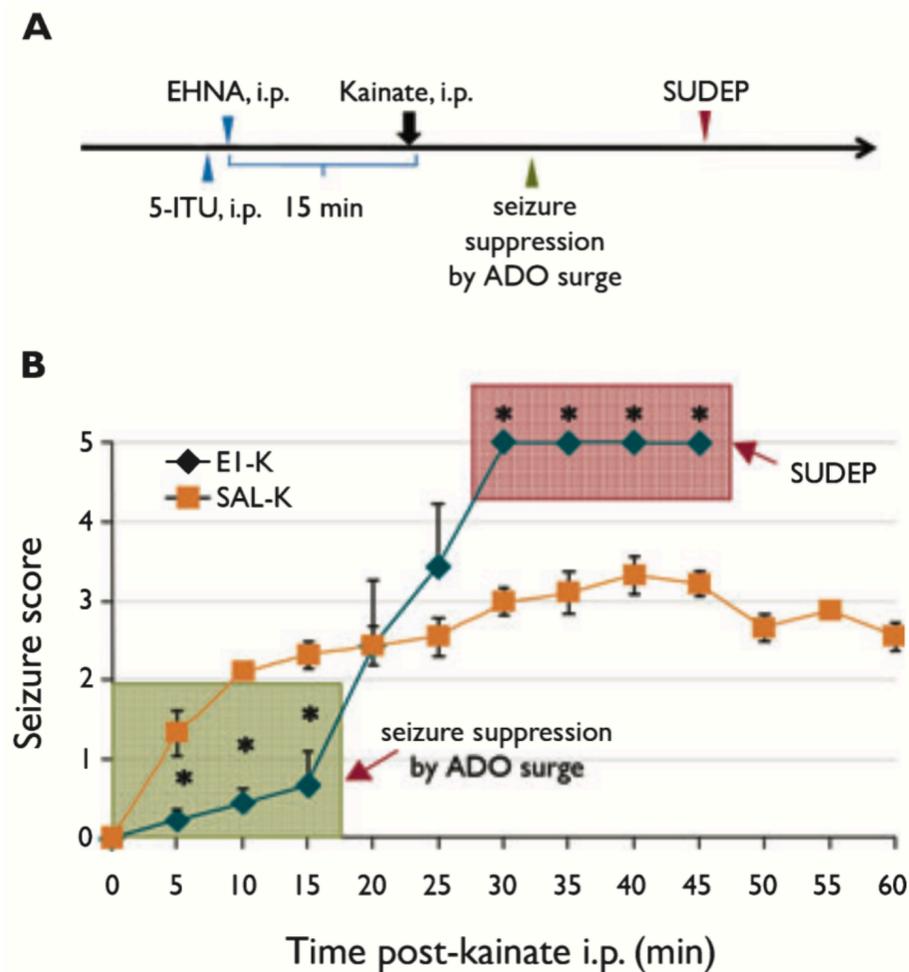
## BRIEF COMMUNICATION

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

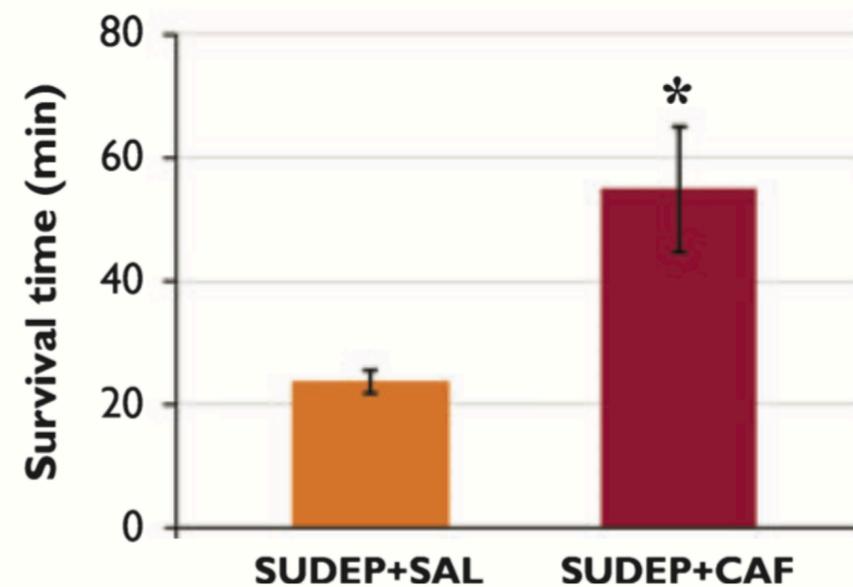
Hai-Ying Shen, Tianfu Li, and Detlev Boison

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

Endogenous anticonvulsant adenosine: mechanism for sz termination

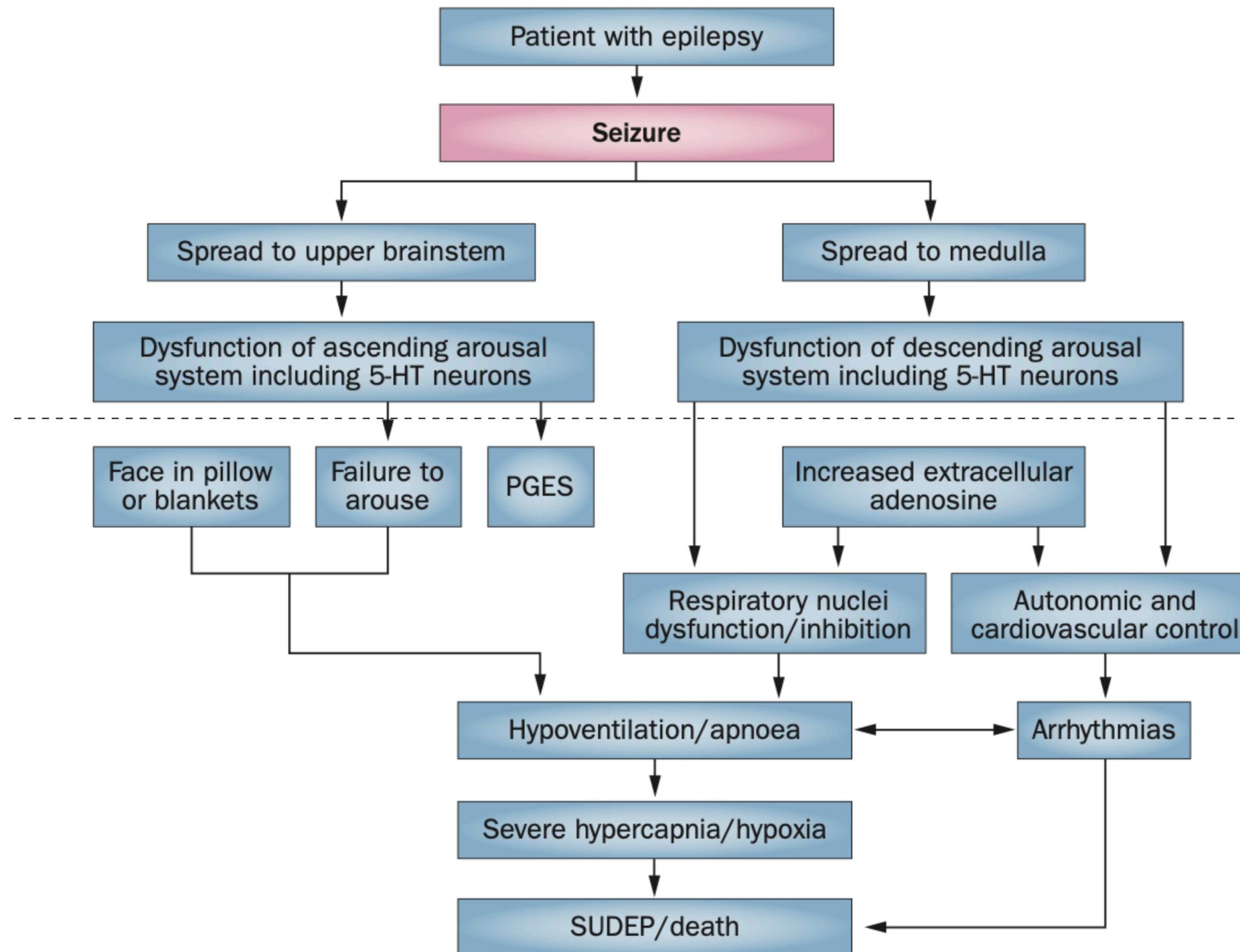


✓ SUDEP is due to overactivation of adenosine receptor



# Pathophysiology remains *incompletely understood*

## No single mechanism established



Genetic factors?

Postictal stage

Postictal brainstem dysfunction

- A. Arousal
- B. Respiratory
- C. Cardiac

# Summary

- PWE have a small but significant risk of sudden unexpected death (SUDEP)
- Pediatric SUDEPs are more common than suspected
- The most significant risk factor is frequent GTCS
- Risk **NOT** limited to patient with frequent GTCS
- Multiple pathophysiologic may be involved: respiratory, cardiac, arousal system; genetic factors may also play a role