

## Sudden Unexpected Death in Epilepsy (SUDEP)

Daniel Winkel, MD  
 Assistant Professor of Neurology  
 Medical Director of the Emory Epilepsy Clinic  
 Emory University School of Medicine




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## Disclosures

External Industry Relationships	Company Name	Role
Equity, stock, or options in biomedical industry companies or publishers	None	
Board of Directors or officer	None	
Royalties from Emory or from external entity	None	
Industry funds to Emory for my research	LivaNova Clinical Affairs (Legacy Cyberonics)  UCB Biosciences Inc	Site PI for the "ASCEND: Vagus Nerve Stimulation Titration Protocol to Improve Tolerance and Accelerate Adaptation" study  Site PI for the "Open-Label, Multicenter, Follow-Up Study to Evaluate the Long-Term Safety and Efficacy of Brivaracetam Used as Adjunctive Treatment in Subjects Aged 16 Years or Older with Epilepsy" study
Other	None	

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## Roadmap

- Definition
- Diagnosis/evaluation
- Incidence and public health burden
- Risk factors
- Possible mechanisms
- What can we do?

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### Causes of Epilepsy-related Deaths

- Approximately 42,000 deaths are caused by epilepsy annually
  - 2.6-fold increase risk of premature death
  - 24-fold increase compared to young, healthy adults
- Accidents
  - Motor vehicle collisions, drowning, falls, etc
- Status epilepticus
  - Neurotoxicity, complications of intubation and hospitalization, etc
- Mood disturbance
  - Depression/anxiety → suicide
- SUDEP

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### SUDEP – Definition

“The sudden, unexpected, witnessed or unwitnessed, non-traumatic, and nondrowning death in patients with epilepsy, with or without evidence for a seizure, with exclusion of documented status epilepticus, and when post-mortem examination does not reveal a structural or toxicological cause for death.”

Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. *Epilepsia* 1997; 38 (suppl 11): 56–58.

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### SUDEP – Definition

- Patient with epilepsy
- Death occurs unexpectedly, when pt in reasonably good state of health and engaging in benign, normal circumstances
- Death occurs suddenly (minutes)
- No obvious cause (including no status epilepticus)

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### Diagnosis

- One of exclusion
- No signs of trauma, infection, hemorrhage, MI, PE
- Usually unwitnessed (often found dead in bed)
- May be evidence of seizure (e.g. tongue bite), but not required and often absent
- Presumptive diagnosis

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### Evaluation

- Autopsy (complete, including heart and coronary/pulmonary arteries)
  - With unrevealing autopsy: definite SUDEP
  - Without autopsy: probable SUDEP
- Toxicology screen
- Interview with families (circumstances around death?)

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### Incidence

- Sudden death in general population: 1-2 per 10,000
- Among pts with epilepsy: 10-150 per 10,000
  - Referrals to epilepsy centers (eg the Emory population): 50-60/10,000 (= 1 in 183)
  - Surgical candidates: 90/10,000 (= 1 in 111)
  - Surgical failures: 150/10,000 (= 1 in 66)
- 5-18% of all epilepsy deaths
- In some studies, as high as 50% of refractory epilepsy deaths

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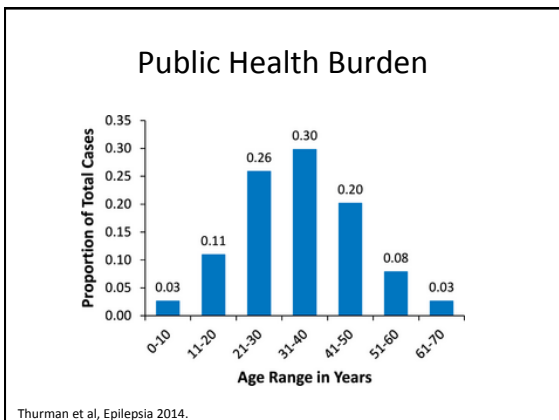
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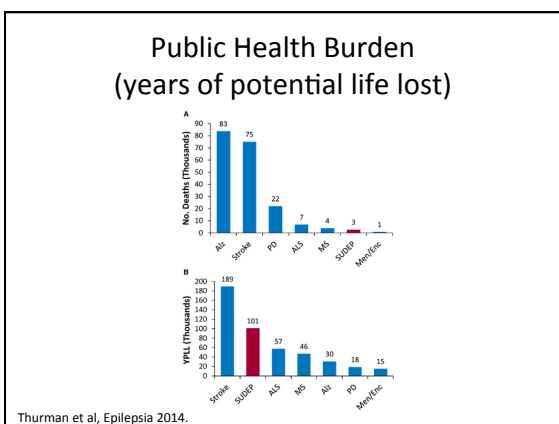
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- ### Risk Factors, general
- Young age
  - Mental retardation
  - Male gender (1.4-fold higher)
  - Black race (as high as 3:1 in some studies)
  - Treatment with antipsychotic meds
  - Alcohol abuse
- Tomson et al, Epilepsia 2005.

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### Risk Factors, seizure-related

- GTCs
- Nocturnal seizures
- High seizure frequency
  - 1-2 GTCs/yr: 3-fold increased risk
  - 3-50 GTCs/yr: 8-9-fold increased risk
  - > 50 GTCs/yr: 15-fold increased risk
- Controlled epilepsy = no increased risk

Tomson et al, Epilepsia 2005.

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### Risk Factors, treatment-related

- Polypharmacy
- Number of AEDs ever taken
- Frequent dose changes
  
- The above likely represents refractory epilepsy rather than medication effect
  - Correlation, not causation
  
- Low AED levels (aka non-adherence)

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### Proposed Mechanisms

- Cardiac
  - Fatal arrhythmia
- Pulmonary
  - Neurogenic pulmonary edema
- Apnea
  - Central vs obstructive
- Role of serotonin?

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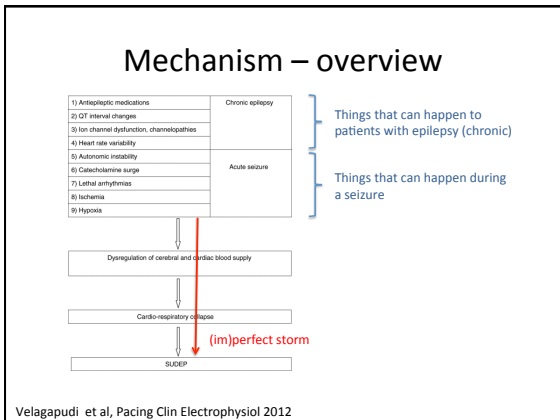
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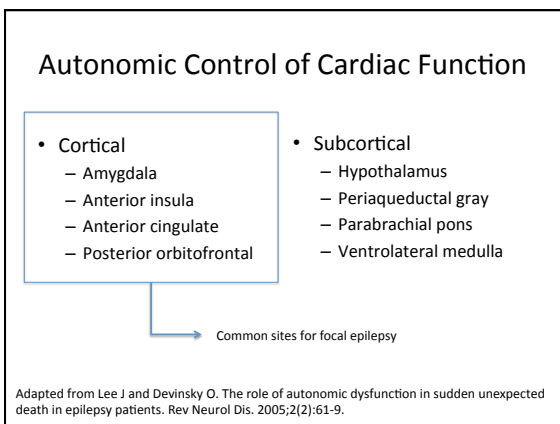
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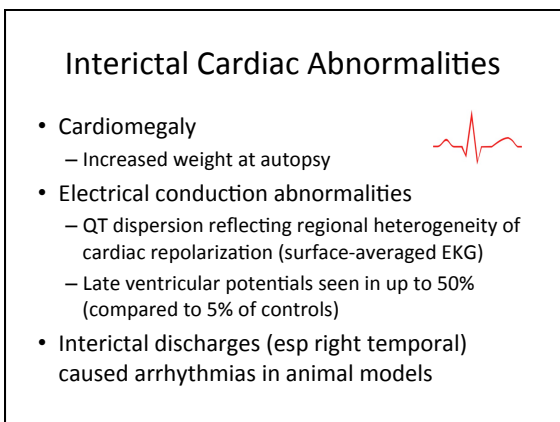
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### Ictal Cardiac Changes

- Well-known pattern of ictal tachycardia
  - Seen as far back as 1939 (Erickson)
- Ictal cardiac abnormalities very common (30-40%)
  - Most common: sinus tachycardia, PACs
  - More malignant: (asystole, sinus pauses, ST-segment elevation or depression, and T-wave inversion) seen in 10-15%

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### Cardiac Arrhythmia Hypothesis

- Seizure begins (involves amygdala/cingulate/insula, etc?)
- Excessive catecholamine outflow
- Collectively, results in irregular heart rate
- Eventual victims of SUDEP have higher ictal tachycardia
- Ictal tachycardia even higher from sleep

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### Ictal Bradycardia

- Ictal and post-ictal bradycardia common as well
  - 6% of seizures
  - 13% of patients undergoing LTVM
- Mechanism less clear
  - Bilateral temporal lobe involvement
  - Parasympathetic activation vs sympathetic inhibition
- Unknown whether self-limiting or causal for SUDEP
  - Role for pacemaker placement?

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### Proposed Mechanisms

- Cardiac
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### Pulmonary Hypothesis

- Most victims of SUDEP found to have pulmonary edema
  - Increased lung volumes from fluid
- Known to occur with generalized seizures
  - Generally reversible (if survivable)
- Not well-elucidated

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### Proposed Mechanisms

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### Apnea Hypothesis

- In sheep, status epilepticus led to rapid death in certain subjects
- In those, there was rapid rise in pCO<sub>2</sub> and fall in pO<sub>2</sub> attributed to apnea

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### Apnea Hypothesis

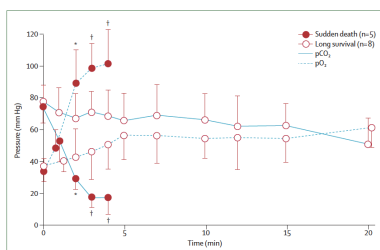


Figure 2: pO<sub>2</sub> and pCO<sub>2</sub> concentrations during seizures in sheep. In experimental status epilepticus in sheep, there is a rapid fall in pO<sub>2</sub> and rise in pCO<sub>2</sub> concentrations before death in animals that died (red circles) compared with those that survived (open circles) attributable to hypoventilation. Reproduced from Johnson and colleagues. \*p<0.05. †p<0.005. pO<sub>2</sub>=partial pressure of oxygen; pCO<sub>2</sub>=partial pressure of carbon dioxide. The error bars represent the standard error.

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### Apnea Hypothesis

- MORTEMUS study (2009)
  - Multicenter retrospective study
  - 160 EMUs surveyed; 147 responded
  - Total of 29 cardiopulmonary deaths reported
    - 16 SUDEPS
    - 9 near-SUDEPs (successful resuscitation)
- Pattern of tachypnea (18-50 breaths/min) +/- tachycardia beginning immediately post-ictally
- After approx 3 min, central apnea followed by cardiac arrest
- Prolonged post-ictal EEG suppression (> 50 sec) may lead to *central* apnea (vs obstructive)

Ryvlin et al, Lancet Neurol 2012

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### MORTEMUS, con't

- Few key points:
  - Immediate ictal to post-ictal tachypnea (+/- tachycardia)
  - Sustained for 1-3 minutes
  - Followed by generalized EEG suppression and combination of apnea and bradycardia (even asystole) – termed “neurovegetative breakdown”
  - Terminal apnea always preceded terminal asystole
  - CPR, when done within the 1-3 minute window, resuscitated all arrests

Ryvlin et al, Lancet Neurol 2012

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### Apnea Hypothesis

- In three mouse strains, oxygenation completely prevented seizure-induced death

Mouse strain	Treatment group <sup>a</sup>	No. mice tested	O <sub>2</sub> <sup>b</sup>	MSS <sup>c</sup>	% Seizure <sup>d</sup>	% Death
D2	I	12	-	3.0 ± 0.0	100	100
	II	18	+	3.0 ± 0.0	100	0 <sup>e</sup>
	III	9	-	3.0 ± 0.0	100	80
	IV	5	+	2.8 ± 0.4	80	0 <sup>e</sup>
	V	21	-	3.0 ± 0.0	100	95
B6SAS	I	36	-	3.0 ± 0.0	100	100
	II	36	+	3.0 ± 0.0	100	0 <sup>e</sup>
	III	12	-	3.0 ± 0.0	100	100
	IV	13	+	3.0 ± 0.0	100	0 <sup>e</sup>
	V	23	-	2.9 ± 0.4	96	91
Primed-B6	I	19	-	1.9 ± 1.3	58	58
	II	27	+	2.0 ± 1.2	56	0 <sup>e</sup>
	III	7	-	2.1 ± 1.1	29	43
	IV	18	+	2.3 ± 1.0	72	0 <sup>e</sup>
	V	27	-	2.3 ± 1.0	67	52

<sup>a</sup>Treatment groups include I, mice treated in air; II, mice treated in oxygen; III, survivors from group II treated 24 h later in air; IV, survivors from group II treated 24 h later in oxygen; V, mice treated in air 1 min after a 2-min exposure to oxygen.

Venit et al, Epilepsia 2004

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### Proposed Mechanisms

- Cardiac
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### Serotonin Hypothesis

- Serotonin enhances respirations in the face of elevated pCO<sub>2</sub>
- Following audiogenic seizures in DBA/2 mice, SSRI reduced incidence of respiratory arrest
- Conversely, cyproheptadine (serotonin antagonist) increased respiratory arrests
- Unfortunately, doses required for this clinical effect are too high to use in people

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### Proposed Mechanisms

- Cardiac
    - Fatal arrhythmia
  - Pulmonary
    - Neurogenic pulmonary edema
  - Apnea
    - Central vs obstructive
  - Role of serotonin?
- } Likely a combination

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### Prevention

- Good seizure control (remember Tomson's data)
  - 1-2 GTCs/yr: 3-fold increased risk
  - 3-50 GTCs/yr: 8-9-fold increased risk
  - > 50 GTCs/yr: 15-fold increased risk
  - 0 GTCs/yr = no increased risk
- Rapid application of O<sub>2</sub>, when available
- First Aid training for family
- Bed alarms? (remember MORTEMUS)
- SSRI? Sleep with O<sub>2</sub>? (remember mice)
- Sleep more upright?
- Pacemaker placement?

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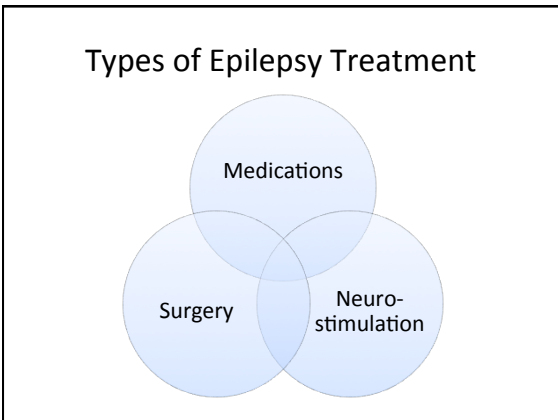
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- ### Ethical Concerns
- We are encouraged to tell
  - Right time?
  - Ever appropriate to not discuss?
  - Best way to raise the issue?

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- ### Resources for Patients
- <http://www.sudepaware.org/>
    - Charity, raising awareness
  - <http://www.epilepsy.com/learn/impact/mortality/sudep/sudep-resources>
    - Brochures for patients with epilepsy and for the bereaved
  - <http://sudep-registry.org/>
    - Family members can provide details of their loved one's death

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## Thank you

### Questions?

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