Plenary 3
What Do We Know about the Factors that Predispose Certain People to Die from a Seizure?
June 24, 2016
1:30 p.m. - 3:30 p.m.
Moderators: Rainer Surges, MD, University of Bonn and Elson So, MD, Mayo Clinic

- Parent Speaker: Trish Barnes

- How Does a Disturbed Autonomic Nervous System Facilitate SUDEP? - Brian Moseley, MD, University of Cincinnati

- Which Genes Could Play a Role in SUDEP? - Alica Goldman, MD, PhD, Baylor College of Medicine

- Are There “Dangerous” and Harmless Seizures? - Philippe Ryvlin, MD, PhD, Lyon University

- Why Do People Die During Sleep? - James Tao, MD, PhD, University of Chicago Medical Center

- Why Don’t People Take Their Meds and the Effect on SUDEP Risk? - Ed Faught, MD, Emory University School of Medicine

- Who Is at Risk for Seizure-related Injuries and Deaths? - Elaine Wirrell, MD, Mayo Clinic

**Panel Discussion:**
- Where are the gaps in knowledge?
- What is the end goal for patients with this research?
- What clinical findings should be explored in the lab?
- What basic findings are ready to translate to the clinic?
Plenary 3: What Do We Know about the Factors that Predispose Certain People to Die from a Seizure?

Moderators:
Rainer Surges, MD, University of Bonn
Elson So, MD, Mayo Clinic

Topics
- What do parents feel about SUDEP? - Trish Barnes
- How does a disturbed autonomic nervous system facilitate SUDEP? - Brian Moseley, MD, University of Cincinnati
- Which genes could play a role in SUDEP? - Alicia Goldman, MD, PhD, Baylor College of Medicine
- Are there "dangerous" and harmless seizures? - Philippe Ryvlin, MD, PhD, Department of Clinical Neurosciences, CHUV, Lausanne
- Why do people die during sleep? - James Tao, MD, PhD, University of Chicago Medical Center
- Why do people not take their meds and how could this affect the SUDEP risk? - Ed Faught, MD, Emory University School of Medicine
- Who is at risk for seizure-related injuries and deaths (other than SUDEP)? - Elaine Wirrell, MD, Mayo Clinic

Disclosure
Rainer Surges
- Bial: Honorary for advisory board
- Cyberonics: Speaker fees
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- Novartis: Speaker fees
- UCB Pharma: Speaker fees
- Springer (publisher): Royalties (book chapter)

Elson L. So
None
How does a disturbed autonomic nervous system facilitate SUDEP?

Brian D. Moseley MD
Assistant Professor
Department of Neurology and Rehabilitation Medicine
University of Cincinnati

Learning Objectives

Following publication in this activity, learners should be able to:
- Understand how SUDEP may be mediated by autonomic disturbances
- Learn about the most common autonomic disturbances during the peri-ictal (seizure-related) period
- Understand why interactions between different autonomic disturbances may be needed to precipitate sudden death

SUDEP & Autonomic Dysfunction

- While the pathophysiology of SUDEP hasn’t been elucidated, seizure-related autonomic dysfunction is possibly responsible
- Autonomic nervous system
  - Part of the nervous system responsible for control of bodily functions not consciously directed
  - E.g. breathing, heart rate, digestive processes, urination
- Two branches
  - Sympathetic – stimulates the body’s “fight or flight response”
  - Parasympathetic – “rest and digest”

Acute Effects of Seizures on Autonomic Function

- Electrodermal activity (EDA) – sympathetically mediated
- Heart rate variability (HRV) – parasympathetically mediated
- EDA surges in the post-ictal period, while HRV is reduced1
- Increases in EDA correlated with increased duration of post-ictal generalized EEG suppression (PGES)
- Decreases in HRV correlated with PGES duration1
- Pediatric patients have greater sympathetic activation and parasympathetic (vagal) suppression following seizures when adjusted for duration of PGES2

Autonomic Dysfunction Involved in SUDEP

- Cardiac disturbances
- Peri-ictal tachycardia, bradycardia, asystole, repolarization (QTc) anomalies, and reduced HRV
- Peri-ictal hypoxemia and respiratory suppression
- PGES

Peri-ictal Tachycardia

- Most commonly observed seizure-related autonomic disturbance, occurring during and/or after a majority of seizures
- Between 57-95% of seizures marked by a rise in heart rate to >98th percentile for age

Peri-ictal Bradycardia

- Heart rate less than the 2nd percentile for age
- Documented in 2-3.7% of seizures

Peri-ictal Asystole

- Absence of the heartbeat for >= 4 sec
- Occurs in less than 0.5% of seizures

Peri-ictal Asystole and SUDEP

- Some cases of SUDEP have involved an ECG showing bradycardia -> asystole
- If asystole was the cause for SUDEP, risk could theoretically be reduced with pacemaker implantation

Link between SUDEP and Peri-ictal Tachycardia

- Higher maximal ictal heart rates found in patients who later died of SUDEP vs controls with refractory partial seizures
- More significant postmortem fibrotic changes in the deep/subendocardial myocardium found in SUDEP cases
- Could be 2.2 myocardial ischemia from repetitive seizures
- Sympathetic overactivity responsible for tachycardia may cause transient dilatation of ventricular walls and left ventricular dysfunction
- If stress induced cardiomyopathy was severe enough to diminish cardiac output, O2 supply during periods of stress might be compromised enough to result in death
Cardiac Pacing Protective Against SUDEP?

- Not necessarily, as cerebral hypoperfusion may promote early seizure termination
- Seizure duration in patients with syncopal ictal asystole, non-syncopal ictal bradycardia, and non-bradycardic seizures:
  - Seizures with ictal asystole are significantly shorter
  - After a GTC, ictal asystole persists

Cardiac Repolarization (QTC) Abnormalities

- Repolarization: return of cardiac cells to resting state
- Repolarization (QTC) abnormalities can facilitate arrhythmias
- Lengthening of the QT interval may result in torsades de pointes (form of polymorphic ventricular tachycardia)
- Shortening of the QT interval can facilitate a re-entrant ventricular tachycardia

Potential QTC Lengthening and Shortening

- Ictal-associated clinically significant QTC prolongation occurs in 4.8%–10.1% of seizures
- Ictal markedly short QT intervals (QTC <=340 ms) observed in 3.6% seizures
- Enhanced QTC shortening and persistent tachycardia reported after secondarily GTCs

The Link Between SUDEP and QTC Changes

- Strengthened by studies invoking shared genetic mutations
- Cardiac depolarization/repolarization anomalies have been documented in SUDEP victims
  - E.g. SCN5A-encoded cardiac Nav1.5 sodium channel mutation
  - E.g. RYR2-encoded cardiac ryanodine receptor/Ca2+ release channel mutation
  - Genes associated with long QT syndromes (e.g. KCNH2) expressed in hippocampal astrocytes

Sudden Unexpected Death of Epileptic Patient due to Cardiac Arrhythmia After Seizure

- Sudden unexpected death (SUD) occurs in an epilepsy patient after a seizure. The etiology of SUD is often unclear, and the immediate cause of death is usually a cardiac origin.
- The mechanism of death remains speculative. The electrocardiogram typically shows a tall and narrow abnormality, and the victim may have a long QT interval, ventricular tachycardia, or ventricular fibrillation.

Heart Rate Variability (HRV)

- Decreased HRV is associated with increased risk of sudden cardiac death
- Such decreases are also documented in people with epilepsy
  - Includes those with chronic temporal lobe epilepsy
  - And Dravet syndrome
HRV and Seizures

- Reduced HRV is likely secondary to seizure-related reductions in cardiac sympathetic innervation
- Cardiac [123I]metaiodobenzylguanidine (MIBG) uptake is reduced in people with chronic TLE versus healthy controls
  - Such changes may increase cardiac sensitivity to adrenergic stimulation
  - This increases the risk of catecholamine-induced arrhythmias and death

Cerebral Oximetric Changes During Seizures

- Primary/secondarily GTCS marked by lower minimum ictal (4.2% vs 75.8%, p=0.003) and post-ictal %rSO2 values (50.8% vs 70.8%, p=0.004)
  - Trend for higher SUDERP-7 Inventory scores in patients with 1+ recorded seizures with a %rSO2 reduction of >= 20% (7 versus 4.3, p=0.08)
  - Significant preictal increases in %rSO2 observed prior to some recorded seizures
  - Could potentially be used to predict seizure occurrence

**Reduction Hypoxemia**

- Recorded in 25% of seizures
  - At least one seizure in 35% of patients
  - 46.8% of pediatric seizures
  - At least one seizure in 48.9% of children

<table>
<thead>
<tr>
<th>Table 4. Mean latency and duration of desaturations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desaturation (%)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>80-89.9</td>
</tr>
<tr>
<td>70-79.9</td>
</tr>
<tr>
<td>60-69.9</td>
</tr>
<tr>
<td>&lt;60</td>
</tr>
</tbody>
</table>

Cerebral Cerebral Tissue Hypoxemia

- During Ictal cerebral tissue hypoxemia
  - Marked by lower %rSO2 (4% vs 75.8%, p=0.003) and post-ictal %rSO2 values (50.8% vs 70.8%, p=0.004)
  - Trend for higher SUDERP-7 Inventory scores in patients with 1+ recorded seizures with a %rSO2 reduction of >= 20% (7 versus 4.3, p=0.08)
  - Significant preictal increases in %rSO2 observed prior to some recorded seizures
  - Could potentially be used to predict seizure occurrence
Causes of Peri-Ictal Hypoxemia

- Likely a consequence of seizure-related hypoventilation
- Up to 50% of seizures may be marked by central apnea
- 9% marked by mixed or obstructive apnea
- Supported by concurrent rises in end-tidal CO2 during monitored seizures

Causes of Peri-Ictal Hypoventilation/Apnea

- May be secondary to disruption of brainstem respiratory centers by repetitive seizure discharges
- Other potential causes include:
  - Seizure-induced right-to-left shunt
  - Neurogenic pulmonary edema

Potential Ictal Hypoxemia and SUDEP

- Suggested by postmortem and electrophysiologic studies
- Moderate to severe pulmonary edema documented in a majority of SUDEP autopsies
- Up to 80% of witnessed SUDEP cases characterized by respiratory difficulty

Potential Ictal Generalized EEG Suppression (PGES)

- Absence of ictal EEG activity viewed at ≤ 10 microvolts
- Retrospective study of 10 patients who died of SUDEP vs 30 controls: PGES significantly longer in the SUDEP group
- Odds of dying from SUDEP increased when PGES duration >50 seconds
- Odds quadrupled when duration >80 seconds
- Another study failed to show a difference between the presence/duration of PGES in SUDEP vs control groups

PGES and SUDEP

- PGES may result in sudden death via inhibition of brainstem respiratory centers
- Cortical neuronal inhibition may extend to deeper subcortical/brainstem structures
- Interfere with respiratory drive, result in apnea
- In adults, lower mean oxygen saturation nadirs, longer desaturations, and lower end tidal CO2 measurements documented in seizures with PGES

PGES and SUDEP (continued)

- Could be part of a vicious cycle of events culminating in sudden death
- Another possibility: PGES may reflect the severity of seizure-related intrinsic pulmonary dysfunction
- Supported by lack of a significant difference in apnea duration in seizures with and without PGES
References (continued)


Which Genes Could Play a Role in SUDEP

Alica M Goldman, MD, PhD
Department of Neurology
Baylor College of Medicine
Houston, Texas

JUNE 2016

Learning Objectives

- Pathway to discovery of SUDEP genes
- Match between SUDEP physiology and genetics
- Approaches in the discovery of SUDEP genes in patients
- Impact and limitations of genetics in clinical practice

SUDEP Risk Factors

- Epilepsy
- Cardio-autonomic system
- Respiration
- Sleep and arousal functions
- Genes
- Environmental factors

Neuro-respiratory dysfunction and the role of serotonin receptors

Inherited – genetically determined

Most SUDEP occurs in sleep

5HT2A receptors are necessary for CO2 induced arousal

Cardiac arrhythmias and autonomic dysfunction in epilepsy
Modeling epilepsy, arrhythmias, dysautonomia, and SUDEP

SCN1A

21% mortality

Altered Cardiac Electrophysiology and SUDEP in a Model of Dravet Syndrome. SCN1A-R1407X knock-in mice

21% mortality

Scn1a null mice: prolonged QT, RR intervals, arrhythmias, and reduced life span (Lopez-Santiago, 2007; Lin, 2014)

Faulty cardiac repolarization reserve in alternating hemiplegia of childhood broadens the phenotype

Jaffer et al.

Knock-in mouse model of alternating hemiplegia of childhood: Behavioral and electrophysiologic characterization

Humanyan, et al.

Decreased threshold to induced seizures

Apparent increase in seizure related mortality

Search for SUDEP Genes

Patient population

Families

Application of Next Generation Sequencing in SUDEP

coding regions (exomes) of candidate genes:
Targeted exome sequencing ($)

Entire genome:
whole genome sequencing ($$$)
Whole exome sequencing in populations of patients that died of SUDEP: Findings

- There is no one single SUDEP gene that would predispose to SUDEP in every patient.
- The genetic landscape of SUDEP is heterogeneous.
- SUDEP patients tend to carry more detrimental genetic changes.
- Some genes (i.e. SCN1A, DEPD5...) seem to be more commonly found in SUDEP patients.

Pilot analysis of SUDEP genetic landscape in a family

High-resolution molecular genomic autopsy reveals complex sudden unexpected death in epilepsy risk profile

- SCN1A, KCNA1, GABRB3...

SUDEP Risk Factors Interactions

- Epilepsy
- Cardio-autonomic system
- Respiration
- Sleep and arousal functions

Impact on Clinical Care and Practice

- Family involvement at the time of SUDEP is very important.
- Genetic influence in SUDEP has been well established.
- SUDEP genetics is complex.
- Molecular autopsy is possible, although validity of the molecular diagnosis remains to be established.
- Research on SUDEP physiological mechanisms aids in SUDEP gene discovery and gene validation.
Are There “Dangerous” and Harmless Seizures?

Philippe Ryvlin
Department of Clinical Neurosciences, CHUV, Lausanne & Epilepsy Institute IDEE, Lyon

June 2016

Learning Objectives

Following participation in this activity, learners should be able to:

- Know the seizure's characteristics that appear consistently associated with an increased risk of S U D E P
- Know the seizure's characteristics that might be associated with an increased risk of S U D E P

Seizure’s characteristics investigated for S U D E P

<table>
<thead>
<tr>
<th>Publication</th>
<th>Risk Factor studied</th>
<th>OR (95% CI)</th>
<th>Monitored in EMU (MORTEMUS)</th>
<th>Witnessed out of hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesdorffer et al. Epilepsia 2012</td>
<td>3 GTCS/year vs 0</td>
<td>29.6 (12.0–32.8) adjusted</td>
<td>SUDEP N = 15</td>
<td>100%</td>
</tr>
<tr>
<td>Walczak et al. Neurology 2001*</td>
<td>1-2 GTCS/year vs 0</td>
<td>9.9 (7.7–12.8) adjusted</td>
<td>near-SUDEP N = 9</td>
<td>78%</td>
</tr>
<tr>
<td>Langan et al. Neurology 2005*</td>
<td>3 GTCS/year vs 0</td>
<td>4.1 (2.2–9.0) adjusted</td>
<td>SUDEP N = 11</td>
<td>80%</td>
</tr>
<tr>
<td>Langan et al. JNNP 2010</td>
<td>10 GTCS/3 months vs 0</td>
<td>16.8 (7.3–37.4) adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hitiris et al. Epil. Behav. 2007</td>
<td>History of GTCS</td>
<td>3.8 (1.6–9.3) adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surges et al. Epilepsia 2010</td>
<td>OR per each GTCS</td>
<td>2.044 (95% CI 1.00–1.09)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Ryvlin et al. Lancet Neurol 2013
2 Langan et al. JNNP 2010

Disclosure

UCB pharma
Eisai
LivaNova

[Table continues with additional data]
**Generalized tonic-clonic seizures and PGES**

- **GTCS type 1**
  - Bilateral symmetric tonic arm extension
  - N = 51/25 PGES
  - Adjusted OR = 66 (5.4 - 801.8)
  - p<0.001
  - Alexandre et al. Neurology 2013

- **GTCS type 2**
  - No bilateral symmetric tonic arm extension
  - N = 27 - 15% PGES

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**Nocturnal seizures and SUDEP**

- Case-control study of SUDEP & nocturnal seizures 1
  - Nocturnal pattern - seizure night/day = 36% of SUDEP, 17% of controls
  - Associated with an adjusted OR = 2.6 (95% CI 1.3–5.0)

- Cohort study of nocturnal frontal lobe epilepsy 2
  - 103 patients with >5% of nocturnal seizures, 2789 person-years of follow-up
  - 28% with history of GTCS, 6 ± 1/year and 1 ± 1/month
  - SUDEP in a patient with an insular FCD and no GTCS during recent years
  - SUDEP incidence of 0.36 per 1000 person-years (95% CI 0.01 to 2.0)

**Occipital EKG/EEG/SpO2 changes and SUDEP**

- Large number of potential peri-ictal biomarkers of interest
  - Peri-ictal EEG suppression (PGES)
  - QT prolongation, shortening, or increased dispersion (QTd)
  - Increased T wave alternans (TWA)
  - Ventricular late potentials
  - Reduced heart rate variability (HRV)
  - Ictal asystole and apnea
  - Apnea and hypopnea
  - None yet substantiated by reproducible case-control studies 1

**Impact on Clinical Care and Practice**

- GTCS remains the main SUDEP risk factor with OR up to 20
  - As a function of GTCS frequency
  - By directly triggering SUDEP
  - Possibly worse for nocturnal GTCS and GTCS type-1

- Some seizure onset zones might be at higher risk for SUDEP
  - Insula, bilateral and extra-temporal
  - Conversely, NFLE seems to be associated with a low risk of SUDEP

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**Harmless seizures**

- No SUDEP reported to the best of our knowledge in
  - Idiopathic childhood focal epilepsies (BCETCS, BCO)
  - Childhood absence epilepsy

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**Seizure onset zone and SUDEP**

- Insular seizures - case reports
  - 4 SUDEP reported in patients with insular FCD (N=3) or post-operative damage 1–3
  - Near-SUDEP and 2 bradycardia-asystole 4–6

- Temporal seizures — case reports
  - Associated with the occurrence of ictal asystole and ictal apnea 7–9

- Case-control studies of SUDEP and seizure onset
  - Extra-temporal vs temporal: OR = 5.23 (95% CI 1.44–19.17) 10
  - Non-lateralized extra-temporal: OR = 7.94 (95% CI 3.13–20.15) 11

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**Nocturnal seizures**

- Nocturnal seizures – case reports
  - 4 SUDEP reported in patients with insular FCD (N=3) or post-operative damage 1–3
  - Near-SUDEP and 2 bradycardia-asystole 4–6
Why Do People Die During Sleep?

James Tao, MD, PhD.
The University of Chicago, Chicago, IL USA
JUNE 2016

Disclosure
I have nothing to disclose

Learning Objectives

Following participation in this activity, learners should be able to:

• Recognize the risk of SUDEP associated with sleep
• Understand the possible causes of SUDEP attributing to sleep
• Advise the appropriate measures for mitigating the SUDEP risk

The incidence of SUDEP during sleep ranges from 25% to 95%

Of the 1031 cases of SUDEP, 606 (68%) cases of SUDEP were found to have occurred in sleep (defined as those found in sleep or in bed), whereas 425 (32%) cases of SUDEP that occurred in wakefulness.

There is a strong association of sleep with SUDEP, as compared to wakefulness (p<0.001), which suggests that sleep is a significant risk factor for SUDEP.
The incidence of SUDEP during sleep
A systematic review and meta-analysis (Ali and Tao et al. 2015 AES meeting)

In a subset of 114 SUDEP where state of wakefulness was determined in every case.

- 97 (85%) of 114 cases occurred in sleep
- 17 (15%) of cases occurred during awake

Why Do People Die During Sleep?

Hypothesis:

1. Nocturnal seizures are associated with more prominent autonomic dysfunction than diurnal seizures. (Hosotani et al. Epilepsia 2005; Kwon et al. Epilepsia 2007)
2. Nocturnal seizures are associated with prolonged PGES leading to central apnea. (Khosla et al. Ann Neurol 2010; Lamberts et al. Epilepsia 2012; Xu et al.)
3. Postictal impaired arousal and prone position leading to asphyxia and subsequently SUDEP. (Lambs et al. Neurology 2015; Tao et al. Epilepsia 2008)

SUDEP case during sleep (video)

SUDEP case during sleep (EEG recording)
MORTEMUS Study

- SUDEP (14 in the night)
- 64% SUDEP (GDH when blood 1-2 days post death)
- QTc in all SUDEP cases
- Circumflex pattern: QTC in with an initial period (CA only) of at least 10-15 min. Then followed by increased (2) or decreased (1) myocardial injury waves, which may last up to 2 min and final arrests.
- Proposed cause of death:电话 was hypothesized driven heart catastrophe, autonomic imbalance.

Majority (73%) of all (253) reported SUDEP patients were found in prone position: A systematic review and meta-analysis (Liebenthal and Tao et al, Neurology 2015)

SUDEP, suspected positional airway obstruction, and hypoventilation in postictal coma

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Authors</th>
<th>Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIEF COMMUNICATION</td>
<td>Liebenthal and Tao et al.</td>
<td>Neurology</td>
</tr>
</tbody>
</table>

MORTEMUS Study

- Majority (73%) of all (253) reported SUDEP patients were found in prone position: A systematic review and meta-analysis (Liebenthal and Tao et al, Neurology 2015)

Young people (< 40 years) is significantly more likely to die in the prone position (Liebenthal and Tao, Neurology 2015)
There is a strong association of SUDERS occurring in sleep in prone position (87.6%), as compared to SUDERS occurring in wakefulness (52.9%) (p<0.001).

There were 9 out of 10 SUDERS patients died in prone position.

Table 2: Video EEG recorded SUDERS cases

<table>
<thead>
<tr>
<th>Study</th>
<th>A/S</th>
<th>Instance</th>
<th>Postictal</th>
<th>Body position</th>
<th>Postictal TTM</th>
<th>Body position</th>
<th>Postictal</th>
<th>Proposed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose et al. (2015)</td>
<td>AES</td>
<td>1</td>
<td>prone</td>
<td>prone</td>
<td>9 mins</td>
<td>prone</td>
<td>prone</td>
<td>Trigeminal</td>
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<tr>
<td>Reber (2016)</td>
<td>AES</td>
<td>2</td>
<td>prone</td>
<td>prone</td>
<td>8 mins</td>
<td>prone</td>
<td>prone</td>
<td>Trigeminal</td>
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<tr>
<td>Bauver et al. (2016)</td>
<td>AES</td>
<td>3</td>
<td>prone</td>
<td>prone</td>
<td>5 mins</td>
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<tr>
<td>Tao et al. (2016)</td>
<td>AES</td>
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<tr>
<td>Spyropoulos et al. (2016)</td>
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<tr>
<td>Spyropoulos et al. (2016)</td>
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<td>prone</td>
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<td>5 mins</td>
<td>prone</td>
<td>prone</td>
<td>Trigeminal</td>
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<tr>
<td>Spyropoulos et al. (2016)</td>
<td>AES</td>
<td>8</td>
<td>prone</td>
<td>prone</td>
<td>2 mins</td>
<td>prone</td>
<td>prone</td>
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<td>prone</td>
<td>6 mins</td>
<td>prone</td>
<td>prone</td>
<td>Trigeminal</td>
</tr>
</tbody>
</table>

*9/15. Some patients exhibited. Some patients exhibited. Some patients exhibited. Some patients exhibited. Some patients exhibited. Some patients exhibited. Some patients exhibited. Some patients exhibited. Some patients exhibited. Some patients exhibited.

Generalized postictal EEG suppression (PGES)

Improve seizure (GTCs) control

Table 2: Video EEG recorded SUDERS cases

**A perfect storm for SUDERS**

**A putative SUDERS Cascade**

- GTCs
- PGES
- Prone
- SUDERS

**Potential SUDERS Prevention**

- Improve seizure (GTCs) control
- Postictal supervision
- Seizures alarming device
- Anti-suffocation pillow
- Avoid prone sleeping or "Back to Sleep"
Impact on Clinical Care and Practice

- Sleep is a significant risk factor for SUDEP
- People with nocturnal GTCS are at an increased risk for SUDEP
- Aggressive medical or surgical treatment
- Preventing postictal prone position potentially mitigates the SUDEP risk
  - Nocturnal supervision
  - Avoid prone sleeping

Acknowledgements
Why Do People Not Take Their Medications and How Could This Affect SUDEP Risk?

Edward Faught, M.D.
Professor of Neurology, Emory University

JUNE 2016

Disclosure

SK Life Science
UCB Pharma
Acorda
SAGE
Brain Sentinel

Learning Objectives

Following participation in this activity, learners should be able to:

1. Know the magnitude of the problem of nonadherence to antiepilepsy drug therapy
2. Understand that not taking antiepilepsy drugs can be fatal
3. Implement strategies for improving adherence

Postmortem Antiepileptic Drug Levels and SUDEP

1) Postmortem serum AED levels (5):
- 44 SUDEP patients and 44 persons with epilepsy who died of other causes.
- Test: NO DIFFERENCE in number with no detectable levels (13 each), subtherapeutic levels (20 each) and therapeutic levels (21 each).

2) Postmortem hair sample AED levels (6):
- 46 SUDEP patients and 38 nonSUDEP (21 patients, 17 in females) who died of other causes.
- Test: MUCH MORE VARIABILITY among SUDEP group (20.5%) vs nonSUDEP (6.1%), outpatients (10.5%) and inpatients (6.2%).
- Suggests more erratic compliance during the time the hair grew (72 wks).

Because of major inter-individual variability in "therapeutic" drug ranges, postmortem testing has very good evidence for poor medication adherence unless there was comparison levels in same persons before SUDEP

7. GENERAL REF on SUDEP and AEDs: Headorffer OG, Tomsian T. CNS Drugs 2013; 27:113-19

Prescription Record Assessment of Adherence: The RANSOM Study

Research on Antiepileptic Nonadherence and Selected Outcomes in Medicaid
GOAL- to measure nonadherence, and to assess its consequences, in a Medicaid population with epilepsy (3 states, 1997-2006, over age 18, all saw neurologist)

(1) Faught E et al; Neurology 2008; 71:1572-78
Measuring Adherence by Prescription Data

Each patient’s observation period was divided into 90-day quarters, total of 33,000 patients observed:

Results: Mortality – Multivariate Analysis

Nonadherence to AEDs correlates with:
- Increased mortality (3x)
  - and morbidity, including 21% more fractures and 108% more motor vehicle accidents
- Increased costs: 86% more hospitalizations, 50% more ER visits

We must understand factors that drive nonadherence and promote strategies to improve it.

Adherence Measured by Medication Possession Ratio

Of 525,114 treated quarters: 388,564 quarters

- were “adherent” - MPR of >80% (patients had drug to cover at least 80% of days)

Nonadherent quarters: higher percentages of patients ≥ 65 years old, females, and greater mean Charlson Comorbidity Index (an index of systemic illnesses)

Results: Morbidity (Univariate)

**Why is there excess mortality with nonadherence?**

1) We don’t know, because we don’t know the causes of death in populations studied for adherence.

SUDEP is only one of several possible causes for this excess mortality.

However, the excess in morbidity, with increases in fractures, increases in accidents with motor vehicles, and increases in hospital encounters with ED visits and hospitalizations, strongly suggests the mediating factor is an increase in seizures.
Why don't people take their medication?
Characteristics of good (Morisky 4+) vs. poor adherers by self-report: significant differences (7)

1. I forget
2. I don't always have my medication with me
3. I think I can skip a dose without a seizure

Forgetting is the most common patient-reported reason (8)

Unhelpful Physician Ideas about Adherence
1) Most of my patients take their medicines.
2) She doesn't mention missing doses, so she doesn't miss them (don't ask!)
3) This is a socioeconomic problem. People who don't take their medicine are poor and uneducated.
4) There's not much I can do about it.
5) I've done my job- if he doesn't take his medication, it's his own fault!

Helpful Ideas about Adherence
1) Enquiry in a nonjudgmental way- what do you do if you miss a dose of medicine?
2) Memory aids- daily routines, weekly pill containers, family assistance, cell phone/pharmacy reminders
3) Education- why you can apparently skip a dose without a seizure but why you should not!

Impact on Clinical Care and Practice
- Mortality increases with nonadherence to medication: SUDEP is one of several possible reasons
- The most common reason for nonadherence is simple forgetting
- It is part of our job as health care providers to assess and try to improve adherence
- Antiepileptic medications save lives!
Who Is At Risk for Seizure-Related Injuries and Deaths?
Elaine Wirrell MD
Mayo Clinic, Rochester MN

JUNE 2016

Learning Objectives
- What is the magnitude of increased risk of accidental injury in persons with epilepsy?
- What types of injury are most concerning?
- What are the potential factors (epilepsy and other) leading to increased risk?

Magnitude of increased risk?
- European multicenter, prospective cohort study comparing injury rates between:
  - 951 persons with epilepsy (>5 yrs of age)
  - 909 matched controls,
  - Cases/controls followed for 17,484/17,206 PY

  Cases:
  - Mode of onset: 55% focal, 37% generalized
  - Seizure frequency:
    - 83% had seizures in the past 2 yrs
    - 70% had seizures less than monthly

Beghi et al. 2002

Beghi et al. 2002

HR 1.6 (95% CI 1.3, 2.1)
Magnitude of Risk Depends on the Population: Injuries Per 100 PY

<table>
<thead>
<tr>
<th>Population Type</th>
<th>Popn based</th>
<th>Epilepsy clinic</th>
<th>Mult handicap</th>
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<tr>
<td>Beghi et al.</td>
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<td>Neufield et al.</td>
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<td>Nakken and Lossius</td>
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<td>Russell-Jones and Shorvon</td>
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Magnitude of Increase in Accidental DEATH

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<tr>
<th>Study</th>
<th>Population Type</th>
<th>Hospital based cohorts</th>
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<td>Hauser et al.</td>
<td>Population-based</td>
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<td>Raffisson et al.</td>
<td>Population-based</td>
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<td>Nilsson et al.</td>
<td>Hospital-based</td>
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<td>Shackleton et al.</td>
<td>Hospital-based</td>
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Potential Factors Leading to Increased Injury Risk

- **Seizure-Related**
  - Abrupt falls
  - Lack of aura
  - Loss of awareness
  - High seizure frequency

- **Non Seizure-Related**
  - Intellectual disability
  - Physical disability
  - Comorbid ADHD
  - AEDs side effects (cognitive, BMD)

Risk factors for head trauma

- **Generalized seizures** (HR 6.8, 95% CI 1.1, 42.6)

- **Seizures leading to falls**
  - In a study of adults in residential care, head injuries occurred in 1/36.5 seizures overall and in 1/16.5 resulting in a fall
  - 45% required sutures, skull #IC bleed in 0.4%

- **AED side effects**
  - 18% without AED side effects, 23% with 1-2 side effects and 32% with ≥3 side effects (p<0.05)

Head Trauma

- 10% of all accidents in persons with epilepsy
- OR 2.6 (1.2, 5.8), but for NSR only, difference was no longer significant
- 1.7-11% of sz-related HI warrant hospitalization (Beghi 2009)

Fractures

- European Prospective study = no increased risk

Risk factors for head trauma

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Fracture Risk

Vestergaard et al. 2005

- Meta-analysis to assess effects of epilepsy on fracture risk and BMD

Risk Factors for Fractures

- Seizure type:
  - GTCS
  - Lack of aura

- Epilepsy duration:
  - Literature conflicted: Shorter or longer

- AED type:
  - Enzyme inducing
  - Longer duration of use – risk of # increases by 4-6% yearly


Risk Factors for Fracture, cont’d

- Greater # AED side effects
- Motor deficits: gross motor, cerebellar
- Female sex
- Minimal sun exposure


Soft Tissue Injury

- Seizure frequency
  - Abrasions more frequent in active epilepsy or with higher seizure frequency

- Seizure type
  - GTCS

- Greater number of AED side effects
  - higher risk of dental trauma

van den Broek et al. 2004, Buck et al. 1997

Burns

- Retrospective reviews of burn unit admissions show that 1.3-3.7% are seizure-related

- Surveys of adults with epilepsy – 3.7-15.9% sustained a burn due to a seizure

Risk Factors for Burns

- **Seizure type**
  - GTCS ± other sz types
  - CPS ± SGTCs higher risk than GTCS alone
- **High seizure frequency**
- **Absence of neurological impairment**
- **AED adverse effects**
- **Female sex**


Risk Factors for Submersion Injury

- **High seizure frequency**
- **Greater number of AED adverse effects**
- **GTCS**
- **Intellectual disability or co-existing handicap**

(Buck et al. 1997, Kemp et al. 1993, Dieker et al. 1993)

Drowning

- The most likely injury to result in death in PWE
- Most common location is in bath or while swimming
- Most occur while patient is unsupervised

Motor Vehicle Accidents

- **Krauss et al. 1999**
  - 25% of pts with epilepsy had more than one sz-related crash
  - 20% had missed an AED dose just prior to the crash
  - 54% who had a sz-related crash were driving illegally

Motor Vehicle Accidents Evidence-based Reviews

- **Naik et al. 2015**
  - Evidence-based systemic review using AAN methodology
  - Evidence for difference in MVA rates in DWE is inconsistent and inconclusive
- **Classen et al. 2012**
  - Crash and casualty databases: MVAs are not predicted by epilepsy or short SFI (3 vs. 12 mos)
  - Self-reported crashes: epilepsy surgery, longer SFI (6-12 mos), few prior non-sz related crashes and regular AED adjustments are protective
  - Mandatory reporting: does not reduce crashes

Conclusions

- Overall, persons with epilepsy have a slightly increased risk of injury
- Epilepsy type matters! Factors associated with greater risk:
  - High seizure frequency
  - Specific seizure types: GTCS, drops, lack of aura
  - Associated neurological disability
  - Greater AED side effects
Conclusions

• Drowning:
  – injury with highest risk of fatality
  – Most deaths occur in bath or pool, with inadequate supervision

• Fractures:
  – Highest risk with long-term use of enzyme inducing AEDs – esp if multihandicapped and little sun exposure – VITAMIN D supplementation

An ounce of prevention is worth a pound of cure
- Ben Franklin