Prevention via Modifiable Risk Factors
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Columbia University
<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
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<tr>
<td>GSK</td>
<td>Travel grant</td>
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<td>UCB</td>
<td>Advisory board</td>
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Learning Objectives

- Understand the major SUDEP risk factors
- Among the major SUDEP risk factors, understand which are potentially modifiable
Long-Term Mortality in Childhood-Onset Epilepsy

• Cohort study of 245 Finnish children with epilepsy
  – 150 incident
  – 95 prevalent
Long-Term Mortality in Childhood-Onset Epilepsy

- After 40 years of follow-up, 60 subjects had died (24%), 3-fold higher than the expected age- and sex-adjusted mortality in the general population.
- 33 of 60 deaths (55%) were related to epilepsy.
- 18 of 60 deaths (30%) were due to SUDEP:
  - 7 in epilepsy of unknown cause
  - 11 in epilepsy of known cause

Cumulative Risk of Epilepsy-Related Death and SUDEP in Childhood Onset Epilepsy

Predictors of SUDEP in childhood onset epilepsy

• Unadjusted analysis
  – Lack of 5 year terminal remission
  – Remote symptomatic etiology
  – History of status epilepticus
  – Epilepsy onset < 2 years

• Adjusted analysis
  – *Lack of 5 year terminal remission*

Sillanpää and Shinnar, NEJM 2010
Conclusions

• Childhood-onset epilepsy was associated with a substantial risk of SUDEP

• The risk was especially high among those people who were not in remission – therapeutic failures

• The increased risk of SUDEP death is mostly occurring in late teenage to adulthood after many years of seizures

Cause of death after epilepsy surgery

- SUDEP 10
- CANCER 3
- SUICIDE 2
- MVA 1
- PNEUMONIA 1
- MYOCARDITIS 1
- PERIOPERATIVE 1

Sperling et al Annals of Neurology 1999
Mortality in post-surgical patients

- Without seizure recurrence
  - 0 to 0.85 per 1000 person-years

- With seizure recurrence
  - 9.1 to 18.9 per 1000 person-years
Slide not available
Conclusions in Surgical Series

- SUDEP represents 53% of postsurgical deaths
- The risk for death is highest in those who have continued seizures
- This is true for all types of surgery
- These deaths reflect therapeutic failure
SUDEP Risk Factors

- Frequent seizures
- Increased frequency of GTCS
- AED polytherapy
- Long duration of epilepsy
- Younger age at epilepsy onset
- Learning disability
- Nocturnal seizures
- Supervision (protective)

Tomson et al Lancet Neurology 2008; Lamberts et al, Epilepsia 2012
Combined analysis of SUDEP risk factors

- Included the four case-control studies with living controls
  - England (Langhan et al, 2005); Scotland (Hitiris et al, 2006); Sweden (Nilsson et al, 1999); USA (Walczak et al, 2001)
Findings of the combined analysis

• Risk of SUDEP was increased by:
  – GTCS frequency
  – AED polytherapy
  – Long duration of epilepsy
  – Young age at epilepsy onset
  – Male gender
  – Symptomatic etiology
  – LTG therapy
  – IGE
  – Learning disability
  – Alcohol abuse
## Number of AEDs and Number of GTCS per year:

215 cases 827 controls

<table>
<thead>
<tr>
<th>Factor</th>
<th>Crude OR (95% CI)</th>
<th>Adj. OR (95% CI)</th>
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<tr>
<td><strong>GTCS frequency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
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<tr>
<td>1-2</td>
<td>5.1 (3.0-8.6)</td>
<td>6.4 (3.4-12.0)</td>
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<tr>
<td>≥3</td>
<td>15.3 (10.0-23.5)</td>
<td>15.5 (9.2-26.0)</td>
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<tr>
<td>Unknown</td>
<td>5.1 (3.1-8.4)</td>
<td>2.3 (1.2-4.5)</td>
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<tr>
<td><strong>Number of AEDs</strong></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>1</td>
<td>0.6 (0.3-1.2)</td>
<td>0.5 (0.3-0.995)</td>
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<tr>
<td>2</td>
<td>1.5 (0.8-2.8)</td>
<td>0.9 (0.4-1.8)</td>
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<tr>
<td>3</td>
<td>3.8 (2.0-7.4)</td>
<td>2.0 (0.9-4.1)</td>
</tr>
<tr>
<td>≥4</td>
<td>4.0 (1.7-9.3)</td>
<td>1.6 (0.6-4.1)</td>
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</table>

Crude analysis adjusts for data source;  
Adjusted for data source, gender and age at death  
Data from England, Sweden and the US  

Hesdorffer et al, Epilepsia 2012
Number of AEDs and Number of GTCS per year: 159 cases 670 controls

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<tr>
<td>0</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>1-2</td>
<td>6.8 (3.7-12.5)</td>
<td>6.8 (3.7-12.6)</td>
</tr>
<tr>
<td>≥3</td>
<td>19.1 (11.8-31.0)</td>
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<td>2.4 (1.2-4.5)</td>
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<td><strong>LTG therapy</strong></td>
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<tr>
<td>No AED</td>
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<td>1.00 (Referent)</td>
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<td>Other AED</td>
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<td>0.7 (0.4-1.4)</td>
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<td>LTG monotherapy</td>
<td>1.5 (0.4-6.2)</td>
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<td>LTG polytherapy</td>
<td>2.9 (1.4-6.0)</td>
<td>0.95 (0.4-2.2)</td>
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Crude analysis adjusts for data source; Adjusted for data source, gender and age at death. Data from England and the US.

Hesdorffer et al, Epilepsia 2012
Timing of seizures and SUDEP

- SUDEP is sleep-related in 58% of cases and unwitnessed in 86%
- History of nocturnal seizures is associated with sleep-related SUDEP OR=3.6 (1.4-9.4)
- Compared to living controls, a history of nocturnal seizures was more common in SUDEP deaths OR=3.9 (2.5-6.0)
  - Adjustment for established risk factors did not change this finding.

Lamberts et al. Epilepsia 2012
Can we prevent SUDEP?

• If SUDEP is related to seizures, data showing that preventing seizures reduces SUDEP would be important

• Alternatively it is possible that more severe disease is associated with SUDEP but that treating the seizures does not influence that risk
SUDEP risk in adjunctive AEDs compared with adjunctive placebo: A meta-analysis of phase III RCTs

Risk of SUDEP more than 5-fold greater on adjunctive placebo than on adjunctive AED at ‘efficacious’ dose

Risk of other deaths greater on adjunctive placebo but NOT significant
Conclusions on the meta-analysis of phase III RCTs

• Adjunctive AED therapy protects against SUDEP, but not other mortality, compared to adjunctive placebo

• Conclusions are limited to the setting of RCTs where
  – AED compliance is closely monitored
  – Duration of treatment is limited
Impact on Clinical Care and Practice

Monitoring people with epilepsy may offer the opportunity to intervene during a seizure, particularly at night while asleep.
Impact on Clinical Care and Practice

• Preventing seizures appears to be the most effective way to prevent epilepsy-related deaths and SUDEP in particular

• Does not alter the risk benefit for
  – Children and adults with 1 seizure
  – Otherwise normal children with epilepsy DURING childhood, especially benign syndromes
Impact on Clinical Care and Practice

• In adolescence and adulthood, acceptable control is NO seizures unless not feasible

• SUDEP is one of the considerations in advocating early resective surgery in appropriate cases as morbidity and mortality of resective surgery is less than risk of SUDEP in this population
Impact on Clinical Care and Practice

• Randomized clinical trials of AEDs must be redesigned to limit the amount of time that participants stay on adjunctive placebo
References

• Sperling et al unpublished.
• Hesdorffer DC, Tomson T, Benn EKT, et al for the ILAE Commission on Epidemiology; Subcommission on Mortality. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk?: A combined analysis. Epilepsia 2012;53:249-252.