Prevention of Epilepsy

Committee on the Public Health Dimensions of the Epilepsies
Workshop on Public Health Surveillance, Population Health
Research, and Data Collection for the Epilepsies
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Susan T. Herman, M.D.
Assistant Professor of Neurology
Department of Neurology
Beth Israel Deaconess Medical Center
Harvard Medical School
Prevention in Epilepsy

- Causes of epilepsy (epilepsy risk factors)
- Seizure measures
  - First seizure
  - Epilepsy
  - Refractory epilepsy
- Comorbidities
  - Cognitive
  - Psychosocial
  - SUDEP
- Epileptogenesis
# Types of Prevention

(Traditional + IOM Components)

<table>
<thead>
<tr>
<th>Prevention Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention</strong></td>
<td>To reduce new cases <em>(Incidence)</em></td>
</tr>
<tr>
<td><strong>Secondary Prevention</strong></td>
<td>To reduce existing cases <em>(Prevalence)</em></td>
</tr>
<tr>
<td><strong>Tertiary Prevention</strong></td>
<td>To reduce complications <em>(Treatment)</em></td>
</tr>
</tbody>
</table>

- **Universal**
  - Targets entire population

- **Selected**
  - Targets entire subset at high risk

- **Indicated**
  - Targets individuals with early signs of disease / high risk

**Target Condition**

**Complications**
Epileptogenesis

- Initial Precipitating Injury
- Latent period
- Epileptogenesis
- First Unprovoked Seizure
- Recurrent seizures
- Epilepsy

- Age
- Genetic factors

- Acute Symptomatic Seizures

- Issues
  - Identification of etiology
  - Misclassification
  - Early seizures
  - Use of AEDs
  - Therapeutic window
  - Factors predicting outcome

- Easily controlled
- Comorbidities
- Refractory epilepsy
Prevention vs. Prophylaxis

- Prevention
  - Avoids the development of a disease by applying measures before it occurs

- Prophylaxis
  - Process of guarding against the development of a specific disease by an action or treatment that affects pathogenesis
AEG Study Design

Eligible

Randomize

Treatment 1

Treatment 2

Placebo

O F F D R U G

Observation

Enrollment window

Treatment

O F F D R U G
# Epilepsy Prophylaxis Vs. Epilepsy Treatment Trials

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of seizures</td>
<td>2-30%</td>
<td>70-100%</td>
</tr>
<tr>
<td>Sample size (50% decrease in epilepsy)</td>
<td>&gt; 200</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Timing of treatment</td>
<td>Unknown</td>
<td>Continuous</td>
</tr>
<tr>
<td>Duration</td>
<td>&gt; 1 year</td>
<td>Days to months</td>
</tr>
<tr>
<td>Post-therapy observation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical endpoint</td>
<td>Time to 1\textsuperscript{st} seizure</td>
<td>Seizure count</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time to n\textsuperscript{th} seizure</td>
</tr>
<tr>
<td>Diagnostic certainty</td>
<td>Low</td>
<td>High</td>
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</table>
Trials of Antiepileptogenesis Using AEDs

Proportion with seizures

Treatment stopped

Months

Time to 1st seizure

Placebo
Anticonvulsant
Antiepileptogenic
## Epilepsy Prophylaxis Trials: Head Injury

<table>
<thead>
<tr>
<th>Ref</th>
<th>Active</th>
<th>Control</th>
<th># pts</th>
<th>Timing</th>
<th>Length treatment</th>
<th>Length follow-up</th>
<th>Late seizure rate (%)</th>
<th>RR, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birkmayer 1951</td>
<td>PHT</td>
<td>No Tx</td>
<td>100</td>
<td>Unclear</td>
<td>4 yrs</td>
<td>Unclear</td>
<td>6*</td>
<td>51*</td>
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<tr>
<td>Pechadre 1991</td>
<td>PHT</td>
<td>No Tx</td>
<td>86</td>
<td>24 hrs</td>
<td>3/12 mos</td>
<td>24 mos</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>Marshall</td>
<td>PHT/PB</td>
<td>Placebo</td>
<td>154</td>
<td>48 hrs</td>
<td>6 mos</td>
<td>18 mos</td>
<td>24*</td>
<td>16*</td>
</tr>
<tr>
<td>Brackett 1979</td>
<td>PHT/PB</td>
<td>Placebo</td>
<td>49</td>
<td>12 hrs</td>
<td>6 mos</td>
<td>18 mos</td>
<td>14*</td>
<td>39*</td>
</tr>
<tr>
<td>McQueen 1983</td>
<td>PHT</td>
<td>Placebo</td>
<td>164</td>
<td>1 wk</td>
<td>12 mos</td>
<td>24 mos</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Locke 1996</td>
<td>PHT</td>
<td>Placebo</td>
<td>146</td>
<td>12 hrs</td>
<td>6 mos</td>
<td>18 mos</td>
<td>1*</td>
<td>8*</td>
</tr>
<tr>
<td>Locke 1996</td>
<td>PB</td>
<td>Placebo</td>
<td>163</td>
<td>12 hrs</td>
<td>6 mos</td>
<td>18 mos</td>
<td>3*</td>
<td>8*</td>
</tr>
<tr>
<td>Penry 1979</td>
<td>PHT/PB</td>
<td>Placebo</td>
<td>125</td>
<td>12 hrs</td>
<td>18 mos</td>
<td>36 mos</td>
<td>23*</td>
<td>13*</td>
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<tr>
<td>Glotzner 1983</td>
<td>CBZ</td>
<td>Placebo</td>
<td>11</td>
<td>12 hrs</td>
<td>24 mos</td>
<td>24 mos</td>
<td>27</td>
<td>33</td>
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<tr>
<td>Young 1983</td>
<td>PHT</td>
<td>Placebo</td>
<td>244</td>
<td>24 hrs</td>
<td>18 mos</td>
<td>18 mos</td>
<td>12</td>
<td>11</td>
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<tr>
<td>Manaka 1992</td>
<td>PB</td>
<td>No Tx</td>
<td>126</td>
<td>1 mo</td>
<td>35 mos</td>
<td>60 mos</td>
<td>16</td>
<td>11</td>
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<tr>
<td>Temkin 1990</td>
<td>PHT</td>
<td>Placebo</td>
<td>404</td>
<td>24 hrs</td>
<td>12 mos</td>
<td>24 mos</td>
<td>27</td>
<td>21</td>
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<tr>
<td>Temkin 1999</td>
<td>VPA</td>
<td>PHT</td>
<td>379</td>
<td>24 hrs</td>
<td>1/6 mos</td>
<td>24 mos</td>
<td>20</td>
<td>15</td>
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<tr>
<td>Temkin 2007</td>
<td>Mg (low)</td>
<td>Placebo</td>
<td>409</td>
<td>8 hrs</td>
<td>5 days</td>
<td>6 mos</td>
<td>9</td>
<td>6</td>
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## Epilepsy Prophylaxis Trials: Other Risk Factors

<table>
<thead>
<tr>
<th>Ref</th>
<th>Active</th>
<th>Control</th>
<th># pts</th>
<th>Late seizure rate%</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Active</td>
<td>Control</td>
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<tr>
<td><strong>Febrile seizures</strong></td>
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<td></td>
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<tr>
<td>Rosman 1993</td>
<td>DZP</td>
<td>Placebo</td>
<td>406</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Knudsen 1996</td>
<td>DZP</td>
<td>No Tx</td>
<td>289</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Wolf 1989</td>
<td>PB</td>
<td>No Tx</td>
<td>355</td>
<td>6</td>
<td>1</td>
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<tr>
<td><strong>Brain tumor</strong></td>
<td></td>
<td></td>
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<td></td>
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<td>Glantz 1996</td>
<td>VPA</td>
<td>Placebo</td>
<td>74</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>Franceschetti</td>
<td>PB</td>
<td>No Tx</td>
<td>29</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Forsyth 2000</td>
<td>PHT</td>
<td>Placebo</td>
<td>100</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Franceschetti</td>
<td>PHT</td>
<td>No Tx</td>
<td>24</td>
<td>10</td>
<td>21</td>
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<tr>
<td><strong>Craniotomy</strong></td>
<td></td>
<td></td>
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<td>North 1983</td>
<td>PHT</td>
<td>Placebo</td>
<td>281</td>
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<td>18</td>
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<td>Shaw, Foy 1991</td>
<td>PHT</td>
<td>No Tx</td>
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<td>Shaw, Foy 1991</td>
<td>CBZ</td>
<td>No Tx</td>
<td>153</td>
<td>31</td>
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</tr>
</tbody>
</table>
Seizure Prevention Trials after Traumatic Brain Injury

Temkin et al., J Neurosurg 1999;91:593-600
Limitations of AEG Studies

- Heterogeneous subject populations
- Variable time window for enrollment / treatment
- Inadequate sample sizes
- Overlap of treatment and observation periods
- Variable outcome measures (e.g. inclusion of both early and late seizures)
- Non-compliance, protocol violations, loss to follow-up
- Unblinded or non-randomized treatment assignment
- Limited range of therapies (mostly first generation AEDs) as the prophylactic treatment
  - Not mechanism based
Current Surveillance of Risk Factors for Epilepsy

- National Center for Injury Prevention and Control
  - Guidelines for the Surveillance of Central Nervous System Injury
  - Multi-state surveillance (12)
  - ICD-9 codes for other medical conditions

- Trauma registries (32 states)

- ETHOS (Stroke Treatment Registry)
  - 86 hospitals, 50 participated > 1 year

- Various state and regional stroke surveillance
NINDS Epilepsy Research Benchmarks

- Identify as yet unrecognized causes of epilepsy
- Identify underlying mechanisms of epileptogenesis.
  - Identify how risk factor predisposes to changes in network excitability
  - Identify convergent pathways or mechanisms of epileptogenesis in multiple models and humans
- Identify biomarkers for epileptogenesis
- Identify approaches to prevent epilepsy or its progression
- Test the efficacy of prevention strategies
NINDS Antiepileptogenesis Workshop, August 2010

- Identify new mechanisms
- Proof of concept in animal models
- Target validation in humans
- Preclinical trial (biomarkers)
- Clinical trial
  - Traumatic brain injury
  - Status epilepticus (febrile status)
  - Tuberous sclerosis
  - Dravet’s syndrome
Proposed Directions

- Longitudinal observational studies
  - Parallel data collection methods in animal models and humans
    - Traumatic brain injury
    - Status epilepticus (febrile status epilepticus)
    - Tuberous sclerosis
    - Dravet syndrome
  - Outcomes: late seizures and neurologic outcome
  - Biomarkers: EEG, neuroimaging, genetics, serum and CSF biomarkers
Needs / Recommendations

- Prevention of causes of epilepsy
  - Fetal and neonatal health
  - Seat belts and helmets
  - Treating hypertension, hyperlipidemia, diabetes
  - Prevention and treatment of CNS infections
Needs / Recommendations

- Ability to identify patients at risk
  - Etiology known, clinically obvious
  - Etiology known, clinically silent until first seizure
  - Etiology unknown
    - Screening
- Avoid misclassification
  - Acute symptomatic vs. unprovoked
  - Use of AEDs
  - Definition of epilepsy
Needs / Recommendations

- Find mechanisms of epileptogenesis
  - Data from registries / surveillance / EMRs
    - Risk factors / potential mechanisms
    - Protective factors
    - Potential interventions
- Track changes in risk over time
  - Effect of treatment of other diseases on epilepsy development
  - Include epilepsy as endpoint in all clinical trials / registries of TBI and stroke with follow-up periods > 6 months
Needs / Recommendations

- Ability to recruit patients for clinical trials
  - Educate practitioners, patients, and the general public that epilepsy is a common and important outcome after a variety of brain injuries
  - Assess public and patient attitudes toward preventive therapies
    - Understanding of risk
    - Efficacy
    - Duration of therapy
    - Adverse effects