Possible Future Devices to Treat Epilepsy
Dec 8, 2013

Robert S. Fisher, M.D., Ph.D.
Maslah Saul Professor of Neurology
Stanford University

American Epilepsy Society | Annual Meeting
Disclosure

<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smart Monitor (seizure watch)</td>
<td>Stock options</td>
</tr>
<tr>
<td>Cyberonics</td>
<td>Consulting, research PI</td>
</tr>
<tr>
<td>Advanced Neurometrics (dry EEG)</td>
<td>Stock options</td>
</tr>
<tr>
<td>ICVRx (CSF drugs)</td>
<td>Stock options</td>
</tr>
</tbody>
</table>

American Epilepsy Society  | 2013 Annual Meeting
Learning Objectives

• Learn about technologies potentially useful for treating seizures.

• Increase awareness of neuroengineering, as an underemphasized field.
Prediction

We can predict everything, except the future.

- John Galsworthy, author
- Woody Allen
- Yogi Berra
Therapeutic Devices for Epilepsy

(none are FDA approved)

- Seizure alert systems
- Seizure prediction
- Cooling
- Optical control (optogenetics)
- Targeted lesions
- Drug delivery devices
- Neurostimulation . . . talk by Andy Cole
I Will Not Talk About

- Diagnostic Devices for Epilepsy
- New EEG Technologies
- New Neuroimaging Technologies
- Gene therapy
- Cell transplants and stem cell

“A man’s got to know his limits”
Therapeutic Devices for Epilepsy

- Seizure alert systems
- Seizure prediction
- Cooling
- Optical control (optogenetics)
- Targeted lesions
- Drug delivery devices
- Neurostimulation

The Need
Notify others when a seizure is taking place

Pioneering work by:
- Kramer / Kuzniecky
- Lockman / Olson
- Kuppens
- Conradsen
- Mizrahi
- Nijsen
Rhythmic Movement Through Pixels


“We’re going to run a few tests to pin down the cause of your seizures.”

by T. McCracken modified by R. Fisher
Therapeutic Devices for Epilepsy

- Seizure alert systems
- Seizure prediction
- Targeted lesions
- Cooling
- Optical control (optogenetics)
- Targeted lesions
- Drug delivery devices
- Neurostimulation

The Need
Anticipate a seizure

Pioneering work by:
- Iasemidis
- Sackellaress
- Litt
- Estellar
- Lenhertz
- Elger
- Le Van Quyen
- Osorio
- Haut
- Cook
- Others
Detect

Predict

1 sec

Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Seizure Prediction Approaches

- EEG component frequency analysis
- Accumulated energy in certain bands
- EEG nonlinear “chaos theory”
- EEG synchronicity and correlation
- EEG high-frequency oscillations
- Multiple unit responses
- Optical changes
- Patient behavior and awareness
- Other
Views of patients with epilepsy on seizure prediction devices

Andreas Schulze-Bonhage a,*, Francisco Sales b, Kathrin Wagner a, Rute Teotonio b, Astrid Carius a, Annette Schelle a, Matthias Ihle a

a Epilepsy Center, University Hospital Freiburg, Freiburg, Germany
b Department of Neurology, University of Coimbra, Coimbra, Portugal

EPIELEPSIAE http://www.epilepsiae.eu
Evolving Platform for Improving Living Expectation of Patients Suffering from Ictal Events
A collaborative European effort
Database of ictal events to test prediction
Development of a portable EEG recorder
Clinical trials of seizure prediction are in planning.
Seizure Prediction Scenario

*Beep, Beep, Beep*

You are likely to have a seizure in the next 10 minutes. Please make yourself safe and put a pill under your tongue.

(Currently fantasy, but maybe not for long)
Therapeutic Devices for Epilepsy

- Seizure alert systems
- Seizure prediction
- Cooling
- Optical control (optogenetics)
- Targeted lesions
- Drug delivery devices
- Neurostimulation

The Need: Reversible reduction of activity in a seizing region of brain

Pioneering work by:
- Rothman / Yang / Hill
- Lesser
- Osorio
- Others
BMI 2mM on left parietal cortex

After cooling to 30°C

After rewarming to 37°C

From R.S. Fisher
Will Cooling the Brain be Practical?

- May only cool top of folds
- One side of plate gets hot
- Demands high power
- Is it safe long-term?
- How well will it work?
Therapeutic Devices for Epilepsy

- Seizure alert systems
- Seizure prediction
- Cooling
- Optical control (optogenetics)
- Targeted lesions
- Drug delivery devices
- Neurostimulation

The Need
Controlling brain excitability by implanted fiber-optics

Pioneering work by:
- Karl Deisseroth
- Ed Boyden
- Jin Hyung Lee (fMRI)
- Many others

Bacteria has a gene for a light-sensitive ion channel. When put into brain cells, it causes the transformed brain cells to be sensitive to light.
Optical control of Excitability

1. Organotypic hippocampal culture slices
2. Stimulus train induced bursting (STIB)
3. Orange light reversibly blocks bursting
4. Halorhodopsin

Is Optical Control Feasible?

- Need to localize seizure focus
- Doubly invasive:
  - Injection of gene with virus
  - Fiberoptic implant
- How long will it last?
- Are there unforeseen effects?
Therapeutic Devices for Epilepsy

- Seizure alert systems
- Seizure prediction
- Cooling
- Optical control (optogenetics)
- Targeted lesions
- Drug delivery devices
- Neurostimulation

The Need: Minimally invasive mini-lesions

Pioneering work by:
- Leksell (gamma knife)
- Adler (cyber knife)
- William Fry (ultrasound)
Stereotactic Radiosurgery


36-month follow-up
Seizure-free for prior 12 months:
- 20 Gy: 10 of 17 (59%)
- 24 Gy: 10/13 (77%)
Focused Ultrasound

Delivery of pulsed ultrasound to thalamus reduced bursting from pentylenetetrazol.

Can also be used for lesioning.

Therapeutic Devices for Epilepsy

- Seizure alert systems
- Seizure prediction
- Cooling
- Optical control (optogenetics)
- Targeted lesions
- Drug delivery devices
- Neurostimulation

The Need: Use geography or quick action to improve the therapeutic/toxic ratio

Pioneering work (brain) by:
- Eder
- Anschel
- Oommen
- Serralta
- Ludvig & NYU group
- Rogawski
- Others
Intra-Nasal AEDs

- midazolam
- lorazepam
- clonazepam

<table>
<thead>
<tr>
<th>Time in minutes</th>
<th>Midazolam: A</th>
<th>Diazepam: B</th>
<th>t test for equality of means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval between giving drug and arrival at hospital</td>
<td>3.37 (±2.46)</td>
<td>14.13 (±3.39)</td>
<td>$-12.89$ 48 0.00</td>
</tr>
<tr>
<td>Interval between cessation of seizure and giving drug</td>
<td>3.01 (±2.79)</td>
<td>2.67 (±2.31)</td>
<td>$0.34$ 48 0.05</td>
</tr>
<tr>
<td>Interval between cessation of seizure and arrival at hospital</td>
<td>6.67 (±3.12)</td>
<td>17.18 (±5.09)</td>
<td>$0.10$ 41 0.00</td>
</tr>
</tbody>
</table>

Values are means (±standard deviation)

Inhaling AEDs

Intra-tracheal in mice at 5, 10 and 20 min before PTZ

- propofol
- control vehicle

Paracelsus, a 16th Century philosopher and physician pointed out that the only difference between a drug and a poison is dose.
Several investigators have looked at possible intraparenchymal perfusion trial designs:

- Existing AEDs
- Adenosine
- Neuropeptides
- Others

Issues of penetration, toxicology, efficacy, chronic receptor changes, identifying the best drug.

A company is planning clinical trials of ICV AEDs
# Therapeutic Devices for Epilepsy

- Seizure alert systems
- Seizure prediction
- Cooling
- Optical control (optogenetics)
- Targeted lesions
- Drug delivery devices
- **Neurostimulation**

**The Need:** Reversible neuromodulation

Pioneering work by:
- Heath
- Delgado
- Cooper
- Velasco family
- Osorio
- Boon
- Morrell
- Many others
<table>
<thead>
<tr>
<th>Wear a shirt in which some person has died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nail from the arm of a Malefactor who has been crucified</td>
</tr>
<tr>
<td>Powder of a man’s skull, found in the earth</td>
</tr>
<tr>
<td>The juice of absinthe, fennel or sage</td>
</tr>
<tr>
<td>Three drops of blood from the third rib of a maddened black cat</td>
</tr>
<tr>
<td>Collect thirty pennies from thirty different people, string them on a ribbon around the neck</td>
</tr>
<tr>
<td>Liver of a mouse, roasted in the new moon</td>
</tr>
<tr>
<td>Burn the patient with a red-hot church key</td>
</tr>
</tbody>
</table>