The good, the bad, and the ugly of trials to prevent epilepsy

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• Why antiepileptogenesis trials should be done
• Preventing epilepsy can be accomplished
• Current status of human trials
• Potential candidates for clinical trials
• Problems with human trials
• What an ideal trial would look like
Quiz

• Which one of the following does not belong on the list?
  • Myocardial infarction
  • Cancer
  • Multiple sclerosis
  • Alzheimer’s disease
  • Stroke
  • Epilepsy
  • Huntington’s disease
  • Amyotrophic lateral sclerosis
Quiz

Which one of the following does not belong on the list?

- Myocardial infarction
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- Amyotrophic lateral sclerosis
How can this be?

- Is epilepsy a major medical problem?
- Does epilepsy develop over time?
- Can we identify risk factors?
- Is it possible that we could intervene in the process to prevent the disease?
- Why aren’t we focusing more attention on this issue?
What is the RED syndrome?

Risk for Epilepsy Development
Risk of Epilepsy After Brain “Insult”

- Moderate to severe head injury (25%)
- Intracerebral supratentorial hemorrhage (25%)
- Prolonged or complex FCs (30-50%)
- Brain tumors (40%)
- Stroke (10-20%)
- Meningitis (5%)
- Status epilepticus (>40%)
- Alzheimer’s disease (15-25%)
- Children carrying epilepsy genes (<5% - >75%)

1.4 M/yr
96,000/yr
3.2 M/yr
20,000/yr
800,000/yr
9,000/yr
30-180,000/yr
5.4 M
200,000
Can we really prevent epilepsy?

- Tottering mouse – PGE
- WAG rat – PGE
- Undercut lesion in rat cortex
- Tuberous sclerosis transgenic mouse
- *(TS in children)*
- Status epilepticus in rats
- TBI in rats
Tottering mouse (*Genetic model*)

- Mutation in voltage dependent Ca channel
- Mice develop absence seizures with S/W EEG discharges
- Hyperinnervation of cortex by noradrenergic axons from locus coeruleus
- Destroy axons from LC before seizures develop prevents the development of seizures

Noebels, Nature. 310:409-11, 1984
WAG rat (Genetic model)

- WAG rat develops absence seizures with S/W EEG discharges during adolescence
- Development of seizures also associated with altered Na channel subunit expression
- Treatment with ethosuximide blocks the development of the seizures and the change in Na channel subunit expression
- Ethosuximide can be withdrawn and animals remain seizure free

Blumenfeld et al, Epilepsia 49:400-409, 2008
Undercut neocortex (Acquired model)

- Producing small lesions in rat neocortex by undercutting produces an island of hyperexcitable cortex
- Treatment with tetrodotoxin for periods right after the lesion creation prevents the development of the hyperexcitability
- Treatment with gabapentin for periods right after the lesion creation also prevents the development of the hyperexcitability

Transgenic mice with the mutant TS gene develop focal seizures.

Treatment with Rapamycin prevents the seizures.

Treatment needs to be maintained.

Status epilepticus induced epilepsy in mice
(Acquired model)

• After prolonged pilocarpine induced S.E. mice develop extensive brain damage and develop epilepsy

• Treatment with Rapamycin either before, or after, the S.E. reduces the incidence of epilepsy and reduces the severity in those that develop epilepsy

TBI in rats (Acquired model)

- Cortical fluid percussion injury produces focal seizures in rats after a short delay
- Cooling the traumatized area can prevent the development of epilepsy

D’Ambrosio et al. AES abstracts, 2009
Current status of human anti-epileptogenesis

- Off the radar screen for a long time
- Phenytoin doesn’t work *
- VPA doesn’t work *
- MgSO$_4$ doesn’t work *
- No evidence that CBZ or phenobarbital are effective, but data are not as strong
- Research in this area has been slow

(* Based on one randomized double blind controlled trial)
Stopping Epileptogenesis

- Identify individuals at risk
- Treat before seizures develop
- Treat for defined period
- Endpoints
  - No seizures
  - Fewer seizures
  - Less severe seizures
  - Longer latency to seizures
  - Medication-responsive seizures
- Prevent progression of epilepsy
Disease modification paradigm

Sz occurrence (%)

0 3 6 9 12 15 18 21 24 mos

Placebo
Anticonvulsant
Antiepileptogenic

Treatment stopped
Ideal clinical scenario

- Adults with easily determined high risk condition
- Treat shortly after the “insult”, or at least before epileptogenesis begins
- Non-toxic treatment
- Relatively short treatment period needed
- No concerns about interfering with recovery
- Good method for ascertaining epilepsy
Potential candidates

- Traumatic brain injury
- Intracerebral hemorrhage
- Brain tumor patients
- Tuberous sclerosis
- Other cortical dysplasias or malformations
- Complex febrile seizures or febrile status
- First episode of status epilepticus
- Genetic syndromes causing epilepsy
- Ischemic stroke
- Alzheimer’s disease
Issues

- Which patients with which risk?
- Which drug?
- What endpoints?
  - Sz vs no sz
  - Less severe epilepsy
    - Less frequent szs
    - Less intense szs
    - Not refractory
- How long to treat?
- What protocol?
- Other issues
  - Recovery of function after TBI, ICH, CVA, etc
  - Developmental issues in children
Issues

- What will the FDA/EMA require?
- How safe will the treatment need to be?
How much animal data do we need before we launch a clinical trial?

• Which models?
  • Is status epilepticus a good model for TBI, or for epileptogenesis after other risks?
  • Are rodents an appropriate model?
  • Is epileptogenesis after different kinds of TBI the same?
    - Blood in brain
    - Penetrating injury
    - WM shear injury

• What kinds of results?
  • Eliminating seizures
  • Reducing epilepsy risk
  • Reducing seizure number or intensity or responsiveness to AEDs

• What is the “gold standard” when there are no successful animal trials?
What kinds of clinical trials are needed?

- Do we know how to do these trials?
- Is research in this area as important as basic research in antiepileptogenesis?
- How can it be funded?
- Should it be left to the pharmaceutical industry?
Brief listing of candidate antiepileptogenesis clinical trials with pros and cons
# TBI trials

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Heterogeneous</td>
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<tr>
<td>Defined onset</td>
<td>Difficult population</td>
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<tr>
<td>Known risk</td>
<td>Multiple trauma</td>
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<tr>
<td>3 well done trials in the literature – single center (U. Wash)</td>
<td>Informed consent for early intervention</td>
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<tr>
<td></td>
<td>Mortality</td>
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<td></td>
<td>Recovery of function</td>
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ICH trials

Advantages
- Adults
- Defined onset
- Clear risk (but not well defined)
- Informed consent usually available

Problems
- Older population
- Heterogeneous
- Mortality
- Recovery of function
- Rescue trials trump antiepileptogenesis
TS trials

Advantages
- High risk but not well defined
- Motivated population
- Informed consent possible
- Supportive preclinical data with available drugs

Problems
- Children
- Heterogeneous
- Effect of treatment on development
- Multicenter
- Available drugs are not benign
- Possible need for continuous treatment
Ischemic stroke trials

Advantages
- Adults
- Real risk
- Large numbers
- Informed consent available

Problems
- Heterogeneous
- Risk unknown
- Seizures may be subtle
- Co-morbidities
- Recovery of function
- Neuroprotection trials trump antiepileptogenesis
## Brain tumor trials

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<td>Adults</td>
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<tr>
<td>Real risk</td>
<td>Often present with seizures</td>
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<tr>
<td>Informed consent available</td>
<td>May have tumors for long periods before diagnosis</td>
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<tr>
<td></td>
<td>Progressive lesion</td>
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<td></td>
<td>Anti-tumor treatment trumps antiepileptogenesis</td>
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</table>
Genetic epilepsy trials

Advantages
- Real risk
- Some data available about risk
- Informed consent available
- Motivated population
- Some animal data encouraging
- EEG biomarker
- Benign drugs may be useful

Problems
- Children
- Development
- Skeptical clinicians
- Pure syndromes uncommon
- Requires multicenter trials
One important lesson learned

If you don’t do a trial, you won’t learn how to do it properly
Issues for a clinical trial for preventing epilepsy after TBI

- Which patients
  - Moderate to severe TBI (e.g. GCS ≤ 12)
  - Blood in the brain or SDH
  - Depressed skull fracture
- How hard does one look for preexisting issues or complicating matters
  - Drug use
  - What came first, the LOC or the accident?
  - Legal entanglements
- How large a sample
- What agent to use
- How quickly to treat
  - Hyperacute (hours) & informed consent issues
  - Acute (1-3 days)
  - Subacute (>3 days) – during “latent period”
- What kind of EEG monitoring
- Which endpoints
- How much follow up
- How much functional assessment during recovery
Advantages of performing early clinical trials

- Experience with infrastructure
- Better epidemiology of risk
- Collection of biomarkers
- Development of new tools
- Availability of experienced investigator teams as new developments emerge from the laboratory
- Establishment of network of experienced investigators
- Influence the directions of laboratory studies
- Development of alternative funding sources
- Stimulation of anti-epileptogenesis trials in other areas of risk
A proposal for a clinical trial protocol for preventing epilepsy after TBI

- Multi-center trial
- Moderate to severe TBI
- Continuous EEG monitoring
  (implanted electrodes and remote telemetry)
- Treat quickly
- Treat for several months
- Treat initially with spike suppressing antiseizure agent
- At least 2 year follow up
- Follow MRIs
- Functional assessments
A proposal for a clinical trial protocol for preventing epilepsy after TBI

- Create ongoing consortium of groups in trauma centers
- Develop funding source for long term studies with new protocols ready to roll out when old ones fail
  - No latency
  - No downtime
  - No dispersal of personnel and expertise
- Try to make study as cost-effective as possible
- Continuous data mining
  - Outcomes
  - Surrogate markers
- Ongoing interaction with basic neuroscientists to seek new treatment options
Limitations with current technology

- We cannot detect small, highly localized seizures with surface EEGs
- We cannot monitor electrophysiological activity in deep structures
- We cannot continuously monitor EEG over prolonged periods
- We have no validated biomarkers
A modest proposal for future antiepileptogenic studies

- Spikes
- HFEOs
- Subclinical seizures
- Intelligent device
- Implantable electrodes
- Trauma
- Imaging
- Proteomics
A modest proposal for future antiepileptogenic studies
This kind of protocol could be modified for other at risk groups

- ICH – with or without intracranial recording
- Stroke
- TS – utilizing patient reporting and EEGs
- Febrile status – with new imaging biomarkers
- Genetic epilepsies – EEG biomarkers
Clinical trial

- New Agents
- Assess Risks
- Data Mining
- Basic research
- Biomarkers

Prevent Epilepsy after known risk

Available AEDs
Summary

- Preventing epilepsy in those at risk should be a high priority for basic and clinical research
- Some progress has recently been made in animal models
- Preventing epilepsy is possible
- Clinical trial research is necessary to prevent inordinate delays in translation
- This likely will need new technologies
- Success will require a partnership between academia, the NIH (and possibly other federal agencies that support research), the pharmaceutical industry and the regulatory agencies
“Nothing can come of nothing”

King Lear
William Shakespeare