Epilepsy Research: SLATE

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Disclosures

- Investigator, Stereotactic Laser Ablation for Temporal Lobe Epilepsy (SLATE), Clinicaltrials.gov identifier NCT02844465
- Investigator, RNS™ System Pivotal Clinical Investigation, Clinicaltrials.gov identifier NCT00264810
Why do we need new therapies?

- Decreased life expectancy
  - Estimated 10 years of life lost for people whose epilepsy has a known cause
  - 2 years lost for people with epilepsy if from an unknown cause

- Impaired Quality of Life
  - 5 x less likely to hold a job
  - 3.5-5.8 x as likely to commit suicide
  - 20% of newly diagnosed people with epilepsy feel stigmatized

- High rate of accidental death
  - 6-20% of deaths of people with epilepsy
  - Twice the risk of the general population
Sudden Unexplained Death in Epilepsy (SUDEP)

- Does not include people who have status epilepticus or seizure-related trauma or drowning
- 0.1% person-years of adults with epilepsy to 1.8% per person-yr in patients with >3 generalized tonic-clonic seizures per year
- Between SUDEP and non-SUDEP epilepsy-related deaths, there is ~ 10% mortality rate per decade in adults with 1 generalized tonic-clonic seizure per year

IOM report 2012
Harden et al. Neurol 2017
# Early Identification of Refractory Epilepsy

**Patrick Kwan, M.D., and Martin J. Brodie, M.D.**

**Table 2. Success of Antiepileptic-Drug Regimens in 470 Patients with Previously Untreated Epilepsy.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to first drug</td>
<td>222 (47)</td>
</tr>
<tr>
<td>Seizure-free during continued therapy with first drug</td>
<td>207 (44)</td>
</tr>
<tr>
<td>Remained seizure-free after discontinuation of first drug</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Response to second drug</td>
<td>61 (13)</td>
</tr>
<tr>
<td>Seizure-free during monotherapy with second drug</td>
<td>41 (9)</td>
</tr>
<tr>
<td>Remained seizure-free after discontinuation of second drug</td>
<td>20 (4)</td>
</tr>
<tr>
<td><strong>Response to third drug or multiple drugs</strong></td>
<td>18 (4)</td>
</tr>
<tr>
<td>Seizure-free during monotherapy with third drug</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Seizure-free during therapy with two drugs</td>
<td>12 (3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>301 (64)</td>
</tr>
</tbody>
</table>
Temporal resection for epilepsy

- Can be tailored depending on where critical structures are and where the seizures seem to be coming from
Randomized trial of temporal lobectomy vs. medication

[Graph A] Surgical group (n=40) and Medical group (n=40)
[Graph B] Surgical group (n=40) and Medical group (n=40)

Wiebe NEJM 2001
Improvement in quality of life

Figure 5. Adjusted and Unadjusted Mean Global Scores on the Quality of Life in Epilepsy Inventory-89.

Wiebe NEJM 2001
Surgery
=
Hope of Seizure Freedom
IOM evidence on the underutilization of epilepsy surgery

- There are an estimated 1 million Americans with drug-resistant epilepsy (DRE)
- Epidemiologic data suggest between 100,000-200,000 people with DRE are surgical candidates
- But only about 4,000 surgeries for epilepsy are performed in the US each year
We have effective therapies that are often not used

- In patients found to have temporal lobe epilepsy, SUDEP and other epilepsy-related mortality can be reduced to that of the general population with brain surgery 60% of the time.

- Similarly, T2N0M0 breast cancer mortality at 10 years is reduced with chemotherapy by 10%.

We would never accept not offering chemotherapy to a woman with breast cancer for a 10% improvement in mortality over a decade. Why would we accept not exploring surgery for a person with epilepsy with a similar benefit?
Why do people with epilepsy and their neurologists often not consider surgery?

- Initial benign appearance
- Knowledge gap- inappropriate optimism about seizure reduction
- Inabilities of humans to accurately assess risk
- Barriers to specialists
- Fear of surgery
Risk Assessment Failure

- Loss aversion bias
  - Losses may be twice as powerful as gains
  - Give up a $2 gain to avoid a $1 loss

- Status quo bias
  - You get used to what you’re used to, even if it stinks
  - Doctors, patients and parents get used to terrible epilepsy
9/11/2001: From Frying Pan to Fire

- Four airplanes hijacked
  - 2,996 Americans died
- Over the next year many Americans drove more and flew on airplanes less
- 1,595 more Americans died than usual from 9-11-01 to 9-11-02 from excess MVAs
  - 4 flights/mo; 1 hijacked plane/mo risk of death: 1/540,000/yr
  - MVA 1/7,000/yr
How do we improve this sorry state of affairs

- Better education of clinicians and patients
  - Understanding patient preferences
- Better prediction of who will and won’t do well with surgery
- Improved technology with reduced risks and discomfort
Reducing Discomfort and Risks of Temporal Resection

- Minimally invasive amygdalohippocampectomy
- Stereotactically implant a laser probe into the epileptogenic zone via a 3 mm incision and a twist drill
- Monitor tissue damage in real time with MR thermography
- May reduce the fear of surgery
- Length of stay = 1
- **FDA-cleared** “to necrotize or coagulate soft tissue through thermal therapy. . . in neurosurgery, . . . [and multiple additional named specialties]. . . under MR guidance
Pre-ablation  Real-time damage model  46mm by 17mm  Post-ablation T1+C
Imaging at 1 year
Advantages of Laser Ablation

- Theoretically, should lead to decreased risk of stroke and visual field cuts
- May reduce the fear of surgery
- Decreased length of stay
- Decreased discomfort
- Faster recovery
- Does not preclude standard anterior temporal lobectomy if it fails
Neuropsychological Advantages of Laser Ablation

- Lower risk when compared to open surgery
  - Naming nouns and famous faces in dominant resections
  - Recognizing famous faces in non-dominant resections
  - Preliminary evidence for delayed recall

- May be an option for patients with dominant temporal lobe epilepsy and normal (or near normal) verbal memory
  - Many surgeons would not offer resection to such patients
Disadvantages of Laser Ablation

- Can sometimes be difficult to get a good trajectory
- Difficult for other targets
The SLATE Clinical Study
Stereotactic Laser Ablation for Temporal Lobe Epilepsy

SPONSOR:
- Medtronic Navigation, Inc.

ClinicalTrials.gov Identifier:
- NCT02844465

OBJECTIVE:
- Evaluate the safety and efficacy of the Visualase™ MRI-Guided Laser Ablation System for mesial temporal epilepsy (MTLE)

STUDY DESIGN:
- Prospective, multicenter, controlled single-arm Investigational Device Exemption (IDE)
Study Design

POPULATION:
- Adult subjects with medically intractable MTLE with radiological and electrophysiological evidence consistent with unilateral focal seizure onsets

SAMPLE SIZE:
- 120 treated with the Visualase Procedure

SITES:
- Up to 20 U.S. centers

PRIMARY ENDPOINTS:
- **Safety:** Incidence of qualifying adverse events through 12 months
- **Efficacy:** Seizure freedom, defined as Engel Classification of Postoperative Outcome Class I through 12 months
Eligibility Criteria - Inclusion

- 18 Years and older
- History of drug-resistant mesial temporal lobe epilepsy (MTLE)
- If the subject has a vagus nerve stimulator (VNS), must have failed to achieve sustained seizure freedom with the VNS implanted for at least 6 months
- On stable antiepileptic drugs (AEDs) (and/or stable VNS setting, if applicable) and compliant with medication use
- An average of at least 1 complex partial or secondarily generalized seizure compatible with MTLE per month
Eligibility Criteria - Inclusion

- Seizure symptoms and/or auras compatible with MTLE
- Video EEG shows evidence of seizures from one temporal lobe consistent with MTLE
- MRI has evidence consistent with mesial temporal lobe sclerosis
- Willing and able to remain on stable AEDs (and stable VNS setting, if applicable) for 12 months following the Visualase procedure
- Willing and able to comply with protocol requirements
Eligibility Criteria - Exclusion

- Unwilling or unable to sign the study informed consent form
- Pregnant or intends to become pregnant during the course of the study
- Currently implanted with a device contraindicating MRI
- Progressive brain lesions and/or tumors not associated with epileptic disease state
- History of previous intracranial surgery for treatment of epileptic seizures
- Persistent extra-temporal or predominant contralateral focal interictal spikes or slowing, or generalized interictal spikes on EEG
- Seizures with contralateral or extra-temporal ictal onset on EEG
- Aura and/or ictal behavior suggest an extra-temporal focus
Eligibility Criteria - Exclusion

- MRI evidence of epileptogenic, extra-temporal lesions or bilateral hippocampal damage
- If additional testing has been performed, results are discordant with the seizure focus scheduled for ablation
- Non-compliance with AED requirements
- IQ < 70
- Dementia or other progressive neurological disease
- Unstable major psychiatric illness, psychogenic non-epileptic seizures, or medical illness that would contraindicate the Visualase procedure or affect the neuropsychological assessments
- Participation in other research that may potentially interfere with SLATE endpoint(s)
- Allergy to gadolinium
Patients can still be treated outside the trial based upon the wording of the FDA approval
Thank You!
Phase II: Intracranial Electrode Placement

- Sometimes can not localize electrically through the scalp, temporalis muscles and skull
- Place electrodes directly on the brain
- First done by Penfield in 1939
- Allows for motor and speech mapping outside of the OR
Risks of Grids and Strips

- Expensive: ~$80K per admission
- Neurologic infections (pooled prevalence 2.3%, 95% confidence interval 1.5-3.1)
- Superficial infections (3.0%, 1.9-4.1)
- Intracranial hemorrhage (4.0%, 3.2-4.8)
- Elevated intracranial pressure (2.4%, 1.5-3.3)
- Complication rate is related to number of contacts/cables and duration of implantation

Wiggins et al 1999
Arya Epilepsia 2013
Reducing risks and discomfort: Stereotactic EEG (sEEG)

- Placement of multiple depths
  - Lower complication rates than grids and strips
    - 6.4% risk of serious complication in Bonn series
    - 2.4% risk of asymptomatic hemorrhage in recent report from Cleveland Clinic
    - No bone flap to remove in the case of wound infection

- Can sample deep structures (insula) more easily

- 3D grid sampling more of the cortex

- Not appropriate for mapping speech
  - But, can use sEEG and then do awake mapping in the OR in cooperative patients

Wellmer et al 2012
Gonzalez-Martinez et al J Neurosurg 2014
Stereotactic EEG

- First reported by Talairach in 1974
- More viable with improved imaging and robotics
Robotic placement of sEEG electrodes

- Gives the ability to change targets and trajectories very quickly
  - Reduces an 8 hr case to 1:30
- HFH was the 3rd center in the US with a ROSA robot
What if there are more than one epileptogenic zone or one is within functional cortex where resection would lead to an unacceptable deficit?
Vagus Nerve Stimulation

- Reduces seizure frequency by ≥ 50% in ~50% of patients, with a delayed benefit more than 1 year after surgery
- Although FDA-approved for partial epilepsy in 1997, patients with generalized epilepsy benefit significantly from VNS
- One-quarter of patients do not receive any benefit from therapy
- Unlikely to result in seizure freedom
- VNS should be considered as palliative for patients in whom medical therapy has failed but who remain poor candidates for resection or who continue to experience seizures after resection

Englot J Neurosurg 2011
Neuropace RNS™

Closed loop stimulation akin to a defibrillator for the brain
No more than 2 epileptogenic regions
FDA approved 2014
Neuropace long term results

- Seems to get better over time
- Sustained improvements in QoL
- 97% retention rate
Conclusions

- Uncontrolled epilepsy results in decreased QoL and decreased life expectancy
- Surgery can result in a cure and is safer than continued ineffective medical therapy
- Emerging technologies are likely to allow better localization of epileptogenic zones and make surgery safer
Who should be referred to an epileptologist?

- If your seizures have not been brought under control after three months of care by a primary care provider (family physician, pediatrician), further neurologic intervention by a neurologist, or an epilepsy center if locally available, is appropriate.

- If you are seeing a general neurologist, and your seizures have not been brought under control after 12 months, you should *insist* upon a referral to a specialized epilepsy center with an epileptologist.
What does “under control” mean?

- Zero seizures with altered level of consciousness per year while compliant with medications

- Likelihood of becoming under control after failing adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) is 1%
Stereotactic Radiosurgery

- Seizure-free efficacy rates (65%) at the 2-year follow-up
- Delayed effects with seizure reduction expected at 9–12 months and complete cessation of seizures between 18 and 24 months
- Since patients are young, there is concern about radiation induced malignancy

Regis et al Epilepsia 2004
Neuropsych Testing

- Focal deficits can help with lateralization
  - In general, right is important for visuospatial memory and left for verbal/declarative memory
  - Seizing hippocampus doesn’t work very well
- Important for predicting risk of postoperative neurocognitive deficits
- Psychiatric/ social screening
Wada test- Intracarotid sodium amobarbital

Selectively depress each hemisphere

- localize speech
- determine whether there is a focal memory deficit
- determine whether hippocampus that will not be resected can support memory
FDG-PET

Shows decreased metabolism from epileptogenic zone when measured interictally.
Magnetoencephalography

Magnetic field contour map

MEG results for localization of Epileptic tissue
<table>
<thead>
<tr>
<th>Engel classification</th>
<th>ILAE classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I. Free from disabling seizures</td>
<td>Class 1. Completely seizure free; no auras</td>
</tr>
<tr>
<td>A. Completely seizure free since surgery</td>
<td>Class 1a. Completely seizure free since surgery; no auras</td>
</tr>
<tr>
<td>B. Nondisabling simple partial seizures only since surgery</td>
<td><strong>Class 2.</strong> Only auras; no other seizures</td>
</tr>
<tr>
<td>C. Some disabling seizures after surgery, but free from disabling seizures for ≥2 years</td>
<td></td>
</tr>
<tr>
<td>D. Generalized convulsions w/AED discontinuation only</td>
<td></td>
</tr>
<tr>
<td>Class II. Rare disabling seizures (almost seizure free)</td>
<td></td>
</tr>
<tr>
<td>A. Initially free from disabling seizures, but still has rare seizures</td>
<td>Class 3. 1–3 seizure days/yr; ±auras</td>
</tr>
<tr>
<td>B. Rare disabling seizures since surgery</td>
<td></td>
</tr>
<tr>
<td>C. Occasional disabling seizures since surgery, but rare seizures for the last 2 years</td>
<td></td>
</tr>
<tr>
<td>D. Nocturnal seizures only</td>
<td>Class 4. 4 seizure days/yr – 50% reduction in baseline no. of seizure days; ±auras</td>
</tr>
<tr>
<td>Class III. Worthwhile improvement</td>
<td></td>
</tr>
<tr>
<td>A. Worthwhile seizure reduction</td>
<td>Class 5. &lt;50% reduction in baseline no. of seizure days – 100% increase in baseline no. of seizure days; ±auras</td>
</tr>
<tr>
<td>B. Prolonged seizure-free intervals amounting to &gt;50% of follow-up period, but not &lt;2 years</td>
<td></td>
</tr>
<tr>
<td>Class IV. No worthwhile improvement</td>
<td></td>
</tr>
<tr>
<td>A. Significant seizure reduction</td>
<td>Class 6. &gt;100% increase in baseline no. of seizure days; ±auras</td>
</tr>
<tr>
<td>B. No appreciable change</td>
<td></td>
</tr>
<tr>
<td>C. Seizures worse</td>
<td></td>
</tr>
</tbody>
</table>
PET-MRI merge with segmentation

2D SUV Map
2D Hypometabolism Map [%]
Hippocampus 2D Hypometabolism Map [%]

2D Hypometabolism Cluster Map (95% CL)
2D Hypometabolism Map (95% CL)
Hippocampus 2D SUV Map
Goals of Surgery

- Remove a part of the brain that is causing seizures or is an essential part of the circuit involved with causing seizures
- Seizure freedom
  - Although only 20-30% of those who are seizure free can be completely off medications
- First, do not harm
Who is a good candidate for temporal lobe resection?

- Medically refractory, complex partial epilepsy
- Clear lesion
- Congruent semiology
- Congruent video EEG
- Likelihood of functional deficit is low
  - Non-dominant with poor visuospatial memory
  - Dominant with poor verbal memory
Awake or Asleep?

- Depends on how much of a neocortical excision is planned, although there is also a basotemporal language area.
- Use local, Propofol or Presedex and remifentanyl.
- Bipolar Ojemann stimulator set at 60 Hz with biphase 1.5 msec 4 second trains starting at 2 mA.
- Place 4 contact strip nearby to measure afterdischarges.
- Increase current by 0.5 – 1 mA as you proceed until you see afterdischarges.
- Then back off 1 mA.
- Have cold saline ready in case the patient has a clinical seizure.
- Show patient slide deck and have him/her name objects while checking different areas.
- Check in different languages if multilingual.
- Any resection done within 2 cm of essential naming area should be done with the patient running through the slide deck.

**Fig. 8. Variability in language localization in 117 patients. Individual maps are aligned as described in the text, and cortex is divided into zones identified by dashed lines. Upper number in each zone is the number of patients with a site in that zone; lower number in circle is the percentage of those patients with sites of significant evoked naming errors in that zone. M and S indicate motor (M) or sensory (S) cortex.**
Phase II: Intracranial Electrode Placement

- Sometimes can not localize electrically through the scalp, temporalis muscles and skull
- Place electrodes directly on the brain
- First done by Penfield in 1939
Findings on Monitoring
Mapping

Vein of central sulcus: N20-P20 inversion on SSEPs between 3 and 4

Contact 11: Site of sz onset

Prior resection
Intraop

Vein of central sulcus

Prior resection
Final resection

With endopial emptying preserving the vein
Perirolandic Mapping

- Can be done in the EMU
Perirolandic Mapping

- Similar technique to speech mapping with direct stimulation (gold standard)
- Can be done with the patient asleep with EMG
  - Young children
  - Pts with sleep apnea or other airway issues
- For tumor resections, can do subcortical mapping
  - Generally = or < required cortical current
  - Need to recheck every 2 mm of resection due to short depth of current penetration
What if the epileptogenic zone is functional?

Multiple subpial transections
- Disruption of horizontal cortical interconnections
- Sparing of vertically oriented fibers
- > 95% reduction in sz frequency
  - 71% for generalized
  - 62% for complex or simple partial
- Can be combined with partial resection
  - > 95% reduction in sz frequency
    - 87% for generalized
    - 68% for complex or simple partial
- But 20% complication rate
Multiple Subpial Transections

- Keep to 4-5 mm deep
- Not sharp, esp. when in sulcus
- Avoid cautery
Multiple Subpial Transections

Keep going until electrical abnormalities on ECoG disappear

Morrell JNS 1989
Corpus Callosotomy

Generally considered palliative for atonic seizures

TABLE 3: Overall outcome according to each patient’s most disabling seizure type

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Class A</th>
<th>Class B</th>
<th>FO (%)</th>
<th>Class C</th>
<th>Class D</th>
<th>Class E</th>
<th>UFO (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>drop attacks</td>
<td>24</td>
<td>22</td>
<td>74.1</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>25.8</td>
<td>62</td>
</tr>
<tr>
<td>GTCS</td>
<td>10</td>
<td>7</td>
<td>73.9</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>26.08</td>
<td>23</td>
</tr>
<tr>
<td>GTS</td>
<td>2</td>
<td>1</td>
<td>75</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>tonic adv sz</td>
<td>0</td>
<td>1</td>
<td>33.3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>66.6</td>
<td>3</td>
</tr>
<tr>
<td>myoclonic abs</td>
<td>0</td>
<td>3</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>total</td>
<td>36</td>
<td>34</td>
<td>73.6</td>
<td>19</td>
<td>2</td>
<td>4</td>
<td>26.3</td>
<td>95</td>
</tr>
</tbody>
</table>
Emerging Technologies: MR-Guided Focused Ultrasound

Not FDA approved