Surgical Innovations for Treating Epilepsy

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# Disclosures

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- **Consultant**
  - LivaNova
  - Sunovion

- **Publication Royalties**
  - Up-To-Date

- **Patents Held**
  - Cannabidiol for FIRES

- **DSMB Member**
  - SLATE Trial – SLA for MTS
Potentially Curable Neurologic Conditions

- Migraine
- Parkinson’s disease
- Muscular dystrophy
- Autism
- Stroke
- Multiple sclerosis
- Alzheimer’s disease
- Epilepsy
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Treatment of Epilepsy 2019

- Antiepileptic drugs (AEDs) - >30!
- Epilepsy surgery
  - Resective
  - Ablative
  - Disconnection
- Ketogenic and other diets
- Neuromodulation
  - Vagus Nerve Stimulation (VNS - SenTiva™)
  - Responsive Neurostimulation (RNS - NeuroPace®)
  - Deep Brain Stimulation (DBS)
After adequate trials of at least 2 AEDs, overall seizure-free rates with subsequent treatment trials are dramatically decreased.

Living with Epilepsy

- No seizures/no side effects (15%)
- Not taking AED (3%)
- No answer (2%)
- No seizures/side effects (17%)
- Recurrent seizures/side effects (44%)

(N=760)

Report of a Roper Poll of Patients on Quality of Life. Research Triangle Park, NC: GlaxoWellcome; 1999
### Treatment Goals for Epilepsy

#### Newly Diagnosed
- AED Trial 1 Monotherapy
- AED Trial 2 Monotherapy or Polytherapy

**Treatment Goal**
- Seizure freedom

#### Refractory Epilepsy
- EEG/Video monitoring
- Epilepsy Surgery
- AEDs (Polytherapy)
- Ketogenic Diet
- Neuromodulation

**Treatment Goal**
- Maximize quality of life
- Optimize Long-term seizure control
- Minimize AED side effects
- Maximize adherence
1,000,000 people (35%) in US with refractory epilepsy

~3000 epilepsy surgeries per year

~4000 VNS/RNS implants per year

Epilepsy prevalence in US ~3.4 million

>1,000,000 people (35%) in US with refractory epilepsy

- 150,000 new cases of epilepsy each year
- 50,000 new cases of intractable epilepsy per year

~3000 epilepsy surgeries per year

~4000 VNS/RNS implants per year

A substantial number of people do not receive adequate treatment

Average duration of refractory epilepsy ~20 years at time of surgery
Outcome (Class I evidence)

- Wiebe, Blume, et al (NEJM 2001)
  - RCT: Epilepsy Surgery vs. AEDs
  - 40 patients in each group followed for 1 year
  - Patients seizure-free
    - Surgery group – 58%
    - AED group – 8%
  - Quality of life measures: Surgery > AEDs
  - Complications: Surgery – 4
  - Death: AED – 1
Craniotomy vs Laser Ablation
SLA Protocol

- Framed (>2 years old), stereotactic, avascular trajectory planning to target with 3.2 mm twist drill hole
- MR FLAIR/T1 to confirm applicator entrance to target, and oblique imaging of entire trajectory
- Placement of safety markers on vital nearby structures and test-dosing with laser
- Ablation of target in real-time with automatic and manual shut-off
- Immediate post ablation imaging (DWI/Contrast) confirming target destruction and lack of vascular injury
Cortical Tuber in Tuberous Sclerosis Complex
Placement of Laser Fiber

Oblique Coronal plane

Frame stereotaxis used to localize and place laser applicator
Thermal Ablation of Target

**Laser Dose:**
3 test pulses used to confirm placement of laser applicator prior to ablation.

**Laser ablation:** 1 exposure, 11.25 watts for 90 seconds

**Estimated Damage Area:**
25 x 22 mm
Post-Ablation Enhanced MRI

Ablation

Fiber

ACA

Post-contrast
Post-Ablation Follow-Up

15 months post-ablation
Hypothalamic Hamartoma
Thermal Ablation of Target

**Laser Dose:**
8 watts for 51 seconds

**Estimated Damage Area:**
- Sagittal: 10.5 x 10 mm
- Coronal: 11.4 x 9.2 mm

Temperature limits were set to protect the hypothalamus (above) and basilar artery and optic tract (below). The limit near the hypothalamus shut the laser off at 51 seconds.
Post-Ablation Enhanced MRI

Ablation

Laser Fiber
82% of the HH patients are seizure-free
95% of all patients are discharged home the following morning (<24-hour hospital stay)

Complications:
- **No** cases of diabetes insipidus
- **No** symptomatic hemorrhages or vascular injuries
- **No** white matter or fiber tract injuries
Why Can’t Surgery be Done?

- Multifocal or generalized seizure onset
- Focus of seizure-onset cannot be localized
- Seizure-onset focus involves a critical brain function (eloquent cortex)
  - Vision
  - Language – expressive and receptive
  - Memory
  - Motor
- Patient or family refusal
Vagus Nerve Stimulation (VNS)
VNS Therapy

- FDA approvals 1997
  - Initial FDA on-label indication – to reduce seizures in patients older than 12 years with partial-onset seizures
  - **NEW** FDA on-label indication – to reduce seizures in patients 4 years old and older with partial-onset seizures
  - **NEW** VNS model 1000 - SenTiva™
    - Smaller, more advanced programming, wireless programming wand
# VNS Therapy Generators

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Long-term Outcome in VNS Therapy

Patients with ≥ 50% seizure frequency reduction

No medication changes were allowed during the study period

LABAR (n=269)
- 57% mean follow-up
- 12 MONTHS

GARCIA-NAVARRETE (n=43)
- 63% mean follow-up
- 18 MONTHS

CHAYASIRISOBHON (n=39)
- 64% mean follow-up
- 24 MONTHS

DE HERDT (n=138)
- 59% mean follow-up
- 44 MONTHS

ELLIOTT (n=436)
- 64% mean follow-up
- 59 MONTHS

On-demand Magnet in VNS Therapy

- **Benefits of on-demand magnet stimulation**

- Offers more control for patients and their families

- Initiates on demand stimulation
  - May abort or decrease severity of seizures\(^1\)
  - May improve postictal period\(^2\)

- Stops stimulation
  - Acutely manage side effects

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Evidence for On-demand Magnet Therapy

62% of seizures were terminated or diminished by on-demand magnet stimulation (N=9,482 Seizures)

24% terminated

38% diminished

On-demand magnet stimulation terminates seizure during video-EEG monitoring

Positive Impact to Seizure

Provides responsive stimulation to heart rate increases that may be associated with seizures.

The AutoStim Mode feature:

- Detects rapid heart rate rise
- Delivers automatic stimulation
- Has customizable parameters to meet patients’ needs
- Works in conjunction with normal and magnet mode
Heart-Brain Connection

Ictal discharges to areas of the brain that regulate the autonomic nervous system can impact heart rate²

82% of patients with epilepsy experience rapid heart rate increase associated with a seizure¹


VNS Autostim Detection Algorithm

Video depicts heart rate before, during and after two ictal events

- **Floating Detection Threshold** automatically adjusts to the patient's underlying activity
- **Threshold** is customizable to individual patient needs (20-70%)
Stimulation-associated desynchronization of focal seizure* 20% Threshold for AutoStim

Over 60% of seizures treated ended during automatic stimulation

(28/46 treated seizures from 14 patients)
Typical Seizure for Same Patient

Same patient's typical seizure progression
(without VNS Therapy Automatic Stimulation)

Focal Seizure (not stimulated in this view)
Updates with SenTiva®

- **Software updates:**
  - Heart rate-based seizure detection with closed-loop automated stimulation
  - Seizure detection incorporates rate of rise, position – prone versus supine, and bradycardia
    - Potentially alerts to patients at risk for SUDEP
  - Allows for differential stimulation parameters during daytime and nighttime
  - Allows for preset weekly incremental parameter introduction without having to visit clinic
VNS titration should be well tolerated by majority of patients

- Expect to feel sensation in throat and may cough with each dosage increase and expect to have on-time voice hoarseness
- Dose-related adverse effects typical resolve within days and voice hoarseness is typically gone within a year of treatment

For particularly sensitive patients, there are several options to maximize comfort and tolerability

- Slow down rate of titration
- Reduce signal frequency from 30 Hz to 20Hz
- Reduce pulse width from 500 usec to 250 usec
For immediate control of treatment-related adverse effects – apply the magnet

Magnet can also be used as needed for control of stimulation-related voice changes
- Singing in church
- Giving public presentations

Surgery is a straightforward day surgery procedure that takes ~1 hour

None of the typical drug-related adverse effects – sleepy, drowsy, dizzy, mood/behavior changes, weight changes, blood, liver, renal effects, no allergic reactions
Interpreting VNS Outcome

- Need to give the therapy time – typically 2 years
  - Important for patient and family to have accurate expectations
    - Unlike brain surgery, not going to wake-up seizure-free
- My personal experience in children (>800)
  - 75% of children will have at least at 50% reduction in seizures after 2 years of therapy
  - 11% are seizure-free
  - 25% still have worthwhile benefit with magnet therapy, reducing drug burden, brighter and more alert, less depressed
  - Keep in mind that refractory epilepsy is often a progressive disease – same seizure burden 2 years later can be a dramatic positive outcome
Responsive Neurostimulation (RNS - NeuroPace®)
Responsive Neurostimulation (NeuroPace®)

First closed-loop therapy system

- **Monitors** brain activity continuously
- **Detects** patient-specific patterns
- **Stimulates** automatically

**Records**
- Frequency, timing, and location of electrographic activity
- Over months/years in a naturalistic setting
Responsive Neurostimulation (NeuroPace®)

Cranial neurostimulator connected to one or two leads placed at seizure focus.
Responsive Neurostimulation
Personalized for each individual’s seizure fingerprint

**Step 1: Detection**
Physician identifies and programs neurostimulator to detect patient-specific electrocorticographic patterns.

**Step 2: Stimulation**
Physician programs device to automatically stimulate in response to specific patterns, with the goal of preventing a clinical seizure.
RNS® System Therapy Overview

- **Long-term seizure control**
  - Class I Evidence and long-term follow-up studies
  - 72% median seizure reduction at 7 years\(^1\)
  - 30% achieved ≥90% seizure reduction\(^2\)
  - 16% of patients have seizure free period of ≥ 1 year\(^1\)
  - Significant quality of life and cognitive improvements\(^3,4,5\)

- **Long-term safety, minimal side effects**
  - Reversible therapy, non-destructive to brain tissue
  - Clinical experience represents >1,700 implant years\(^1\)
  - No adverse cognitive effects and no chronic stimulation side effects\(^3,5,6\)
  - Serious adverse event rates comparable to deep brain stimulation for movement disorders\(^6\)

- **Unique window to the brain**
  - Provides long-term ECoG recordings that supplement clinical seizure reports and patient management
  - Data obtained may complement other therapies – medications, resection/laser, etc.

**FDA approved – 11/14/2013**

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RNS System Candidates

- Patients >18 years of age or older
- Refractory to two or more medications
- Partial onset seizures with 1-2 seizure foci
- Patients commonly treated with the RNS System:
  - Bilateral mesial temporal onsets
  - Unilateral mesial temporal onset with risks to memory or language with resection
  - Onset in eloquent (functional) cortex
  - Suboptimal response to VNS or epilepsy surgery
Responsive Neurostimulation

Median % Seizure Reduction

- Year 1 (n=181): 44%
- Year 2 (n=174): 53%
- Year 3 (n=214): 60%
- Year 4 (n=204): 63%
- Year 5 (n=172): 65%
- Year 6 (n=115): 66%
- Year 7 (n=185): 72%

Responsive Neurostimulation

Safety and tolerability

• No stimulation-related adverse effects

• Infection rate
  ➢ 3.7% - mostly soft tissue

• Implant-related hemorrhage rate
  ➢ 2.7% - vast majority were asymptomatic
Supplement Clinical Seizure Reports

RNS System data can reveal trends in detections over time

Line shows trend in number of long episodes over time
Help Assess Effects of Adjunctive Medication

This patient showed sustained reductions in epileptiform activity with levetiracetam.
Lateralization of seizures of MTL onset

[King-Stephens et al., *Epilepsia*, 2015]

In **20% of patients**, the presumed lateralization determined by prior diagnostic testing changed after chronic ambulatory ECoG monitoring.

11 patients presumed unilateral; 7/11 (64%) had bilateral electrographic seizures

71 patients presumed bilateral, 9/71 (13%) had only unilateral electrographic seizures
What Would I Do?

Personal experience

What would I do if I developed epilepsy:

- Try one or two drugs
- See if I could have surgery, preferably with laser ablation
- Then obtain Neuromodulation therapy
  - VNS
  - RNS
Conclusions

- Refractory epilepsy can be a catastrophic disease
- Management should focus on maximizing quality of life – stopping seizures, minimizing adverse effects
- Ability to identify refractory patients early in the disease course is possible – after 2 AED failures
- Non-pharmacologic treatments should be considered as soon as AEDs fail, especially potentially curative ones
- Exciting and innovative new treatment options are rapidly emerging
Thank-you!