What’s New in Epilepsy Treatment?
Treatment Options for Drug-Resistant Epilepsy

Vishwanath Sagi MBBS MPH
University of Louisville
What is Epilepsy?

A seizure (epileptic seizure) is a period of symptoms due to abnormally excessive or synchronous neuronal activity in the brain. Different types of seizures can produce symptoms ranging from abnormal sensation or twitching to loss of awareness to falling and shaking.

A Provoked seizure occurs in the context of an acute brain insult or systemic disorder (Alcohol withdrawal, electrolyte abnormality). The underlying etiology can be treated/reversed.

Epilepsy is a brain disorder characterized by predilection to spontaneous, recurrent unprovoked seizures.

ILAE Official Report, 2014
Incidence and Prevalence

- 65 million people suffer from epilepsy in the world.
- 3.4 million people in the US have epilepsy.
- 180,000 new cases/year.
- 10% of Americans have had or will have a seizure at some point in their lives.
- ~1 in 26 people will develop epilepsy at some point in their lives.
- ~1/3rd of people with epilepsy live with uncontrolled seizures.
Incidence and Prevalence

- Bimodal distribution
- Prevalence 4-10/1000
- Higher in males

- Etiologies

Hauser et al, 1992
Morbidity and mortality

• Seizure related
  – Accidents

• Other
  – Headache
  – Sleep disturbance
  – AED side effects
  – Memory loss
  – Psychiatric (Depression, anxiety, ADHD)
  – Endocrine (hormonal changes)

• SUDEP (Sudden unexpected death in Epilepsy)
  – Refractory epilepsy
  – Highest risk in first 2 years
  – Risk related to seizures NOT medications
Types of Seizures

Focal (Partial onset) seizures
- About 2/3 of drug-resistant patients
- Begins with an electrical discharge in one part of the brain
- While it starts in one area, it can spread to or involve other areas of the brain

Generalized onset seizures
- About 1/3 of drug-resistant patients
- Begins with widespread electrical discharge that involves the entire brain at once
Antiepileptic drugs (AEDs)

**Broad spectrum:**
- Lamotrigine
- Levetiracetam
- Topiramate
- Zonisamide
- Valproate
- Clobazam
- Felbamate
- Primidone
- Phenobarbital
- Perampanel

**Narrow spectrum:**
- Phenytoin
- Pregabalin
- Lacosamide
- Carbamazepine
- Vigabatrin
- Oxcarbazepine
- Tiagabine
- Eslicarbazepine
- Ezogabine
- Rufinamide
What is Drug-Resistant Epilepsy

If you’ve tried 2 anti-seizure medications and still have seizures, you may have drug-resistant epilepsy.

Kwan & Brodie, 2000; Institute of Medicine; Chen, Z. et al 2018

<5% Success Rate
After trying 2 medications, the chance that a 3rd medication will control seizures is <5%.²
Impact on Quality of life

- Refractory Epilepsy
  - Persistent Seizures
  - Neurochemical Changes
  - Increased Mortality, Greater Risk for SUDEP, Comorbidities
  - Restricted Quality of Life
  - Adverse Effects of ASDs
  - Cognitive Problems
  - Educational, Vocational, Social Consequences
  - Mood and Personality Changes

Tang F et al, 2018
All patients with a diagnosis of intractable (drug resistant) epilepsy were considered for referral for a neurologic evaluation of appropriateness for surgical therapy and the consideration was documented in the medical record within the past three years.
When 2 drugs fail

- Medically refractory, Treatment resistant
- Is the diagnosis correct?
  - 25% of patients previously diagnosed with epilepsy who are not responding to drugs are found to be misdiagnosed
- Epilepsy surgery
  - Resective
  - Ablative
- Neurostimulation
  - Vagus nerve stimulation (VNS) for focal or generalized
  - Responsive neurostimulation (RNS) for focal seizures
  - Deep Brain Stimulation (DBS) for focal seizures
- Diets
  - Ketogenic, Modified Adkins
- Epidiolex
- Clinical trials
What’s next??

- EPIDIOLEX
- VNS/RNS
- KETOGENIC DIET
- BRAIN SURGERY
- ANTIEPILEPTIC DRUGS
- DBS
## Facts and misconceptions

<table>
<thead>
<tr>
<th>Misconception</th>
<th>Fact</th>
</tr>
</thead>
<tbody>
<tr>
<td>All drugs need to be tried.</td>
<td>The chance of seizure remission is &lt;10% after 2 drugs have failed.</td>
</tr>
<tr>
<td>Normal MRI is a contraindication to surgery.</td>
<td>Other techniques often detect a single epileptogenic zone in patients with normal MRIs.</td>
</tr>
<tr>
<td>Surgery is not possible if eloquent cortex is involved.</td>
<td>The risk–benefit ratio can be individually evaluated.</td>
</tr>
<tr>
<td>Surgery will make memory worse if there is an existing memory deficit.</td>
<td>Poor memory usually will not get worse and may improve.</td>
</tr>
<tr>
<td>Low IQ is a contraindication to surgery.</td>
<td>Individuals with low IQ may benefit from remission or reduction in seizures.</td>
</tr>
</tbody>
</table>
Comprehensive Epilepsy Centers (CEC)

You should seek specialized care if you have failed 2 medications.

Team of Experts

• Epileptologist
• Neurosurgeon
• Neuropsychologist
• Epilepsy nurse

Only 1 in 5 patients with refractory epilepsy are being seen at a CEC.
Epilepsy Monitoring Unit (EMU)

Detailed assessment of seizures and EEG changes by Epileptologist

- Typically involves weaning off AEDs
- LOS 3-5 days, can be longer
- Skilled nurse and technicians

- Continuous video EEG monitoring to localize seizure onset areas in the brain
CEC workflow

1. Initial evaluation by Epileptologist
2. Epilepsy monitoring Unit (EMU) MRI Brain
3. Epilepsy surgery Conference
4. Other tests as needed fMRI WADA Neuropsych Ictal SPECT PET
5. Epilepsy Surgery Or VNS/RNS Or DBS
Pre-surgical work up

- MRI – Identify epileptogenic lesion
- Functional MRI (fMRI)- language and motor localization
- Ictal SPECT- Identify seizure onset area
- PET Scan- identify any hypometabolic regions of brain
- WADA- Determine language and memory lateralization
- Neuropsychology testing- Identify and localize memory abnormalities
- Magnetoencephalogram (MEG)- Identify active areas
Intracranial EEG monitoring
Types of Epilepsy surgery

Resection

• Temporal lobectomy
  - Standard
  - Selective amygdalohippocampectomy

• Lesionectomy

• Corpus callosotomy

• Functional hemispherectomy

Ablation

• Laser Interstitial Thermal Therapy (LITT)

~20% can discontinue drugs post-op
Temporal Lobectomy

Temporal Lobectomy

Laser therapy

Wyllie’s Treatment of Epilepsy, 2015
https://physician-news.umiamihealth.org/laser-therapy-shows-promise-for-patients-with-refractory-epilepsy/
Seizure freedom with surgery

- Depends on length of follow-up after surgery
- Depends on if lesional or not (findings on MRI)
  - Lesional temporal lobe resection ~ 80%
  - Mesial temporal sclerosis ~ 70%
  - Non-lesional temporal lobe ~ 60%
  - Lesional extra temporal resection ~ 60%
  - Non-lesional extra temporal resection (frontal/Occipital/Parietal) ~<50%
  - Anti epileptic medication <5%
VNS- Who’s a good candidate?

- Drug-resistant focal epilepsy where surgical resection of the focus is not possible (Seizures unlocalizable or multifocal)
- Drug-resistant generalized epilepsy (not FDA approved indication)
- Electrodes are surgically implanted around the left vagus nerve and connected to the pulse generator in the chest or abdomen
- Discharges the same day
VNS- Practical info

- Patient is getting constant intermittent stimulation
  - 30 seconds ON, 5 minutes OFF (~2.5 hours of stimulation daily)
  - Extra with magnet swipe and with tachycardia with 106 device
- Interrogate device, program, and interrogate again.
- Turn the device off by setting currents to zero for MRI.
- Battery lasts 4-7 years.

Scan Conditions - Latest VNS Therapy technology

No special MRI equipment/collars required

* Patient with implants in other locations must follow device scan conditions.

https://us.livanova.cyberonics.com/patient-resources
Seizure outcomes with VNS

- Average decrease in seizures by 28 percent in first three months.

- Improved quality of life (improvements in alertness, attention, memory and concentration)

- Reduced SUDEP rates

Patients experiencing a >=50% seizure frequency reduction

The Vagus Nerve Stimulation Group, 1995
Morris and Mueller, 199
Neuropace (RNS)
Who is a good candidate?

- Adult patient with intractable focal epilepsy
- Not a surgery candidate
  - Seizure onset zone may be eloquent cortex
  - Multifocal or bilateral foci (up to 2)
- Failed prior epilepsy surgery
RNS System Placement Procedure

- The neurostimulator is placed within a small tray in the skull.
- **It does not touch the brain.** It’s underneath your scalp and not visible to you or anyone else.
- Leads (tiny wires) are placed at the seizure focus or foci.
- Typically 1-2 night hospital stay
- The battery in the RNS-300M Neurostimulator is estimated to last about 4 years, and the battery in the RNS-320 Neurostimulator is estimated to last about 8 years.
RNS- Practical info

- Patient downloads data daily and can be viewed online
- Swipes magnet to save EEG data associated with clinical seizures
- Magnet does not activate device like VNS
- Only gets stimulation when a seizure is detected
- Nondestructive, does not preclude later surgery

**Implantable Device**
The neurostimulator and leads monitor and respond to your brain activity to stop seizures, often before they start.

**Remote Monitor and Wand**
These are used at home to collect information from your neurostimulator.

**Patient Data Management System (PDMS)**
Secure database that allows your doctor to review electrical activity and seizure patterns recorded by your neurostimulator.
RNS System Monitors & Responds to Your Brain’s Unique Seizure Activity

Monitors your brain activity twenty-four seven

Detects unusual activity that can lead to a seizure

Responds with a small electrical pulse to prevent a seizure from occurring
RNS- Circadian Patterns

Histogram data demonstrate nocturnal changes in cortical excitability.

<table>
<thead>
<tr>
<th>Week by Hour Histogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>(normalized average number of detected episodes per hour for the last 12 weeks)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date Range</th>
<th>Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/07/16 - 11/13/16</td>
<td>12am - 11pm</td>
</tr>
<tr>
<td>11/14/16 - 11/20/16</td>
<td>12am - 11pm</td>
</tr>
<tr>
<td>11/21/16 - 11/27/16</td>
<td>12am - 11pm</td>
</tr>
<tr>
<td>11/28/16 - 12/04/16</td>
<td>12am - 11pm</td>
</tr>
<tr>
<td>12/05/16 - 12/11/16</td>
<td>12am - 11pm</td>
</tr>
<tr>
<td>12/12/16 - 12/18/16</td>
<td>12am - 11pm</td>
</tr>
<tr>
<td>12/19/16 - 12/25/16</td>
<td>12am - 11pm</td>
</tr>
<tr>
<td>12/26/16 - 01/01/17</td>
<td>12am - 11pm</td>
</tr>
<tr>
<td>01/02/17 - 01/08/17</td>
<td>12am - 11pm</td>
</tr>
<tr>
<td>01/09/17 - 01/15/17</td>
<td>12am - 11pm</td>
</tr>
<tr>
<td>01/16/17 - 01/22/17</td>
<td>12am - 11pm</td>
</tr>
<tr>
<td>01/23/17 - 01/29/17</td>
<td>12am - 11pm</td>
</tr>
</tbody>
</table>
Assess Effects of Medication

Histogram data demonstrate sustained reduction in seizure frequency with addition of an antiseizure drug.
RNS System Median Seizure Reduction Improves over Time

73% median seizure reduction at year 8*

*Combined trial outcomes include data from Feasibility, Pivotal (randomized, double-blinded, controlled), and Long-Term Treatment (open label, prospective) Trials. Long-Term Treatment Trial was not powered to drive conclusions of clinical significance. Gwinn R, Morrell MJ, and RNS System Investigators, Long-term safety and efficacy of responsive brain stimulation in adults with medically intractable partial onset seizures, American Epilepsy Society Poster, 2017.
Quality of Life Improvements with the RNS® System

6 MONTHS OF SEIZURE FREEDOM reported by nearly 30% of patients

- Physical health
- Cognitive function
- Mental health
- Seizure worry

Neuromodulation Devices for Epilepsy

These therapies for drug-resistant epilepsy work differently.

**BRAIN-RESPONSIVE STIMULATION**

- **Where** stimulation is delivered
- **When** stimulation is delivered
- **Amount** of stimulation delivered
- **Stimulation side effects**

**Targets the seizure focus in the brain**

- Responds to brain activity, where your seizures start
- <6 minutes/day of stimulation
- No chronic stimulation side effects

2. Heck, CN, 2014
Defining the care pathway

Medically Refractory Seizures

Can be localized?

How many foci?

Safe to resect?

Low cognitive risks?

Will it be curative?

Patient willing?

Resective Surgery or Ablation

YES

NO

Safe to resect?

NO

Low cognitive risks?

NO

Will it be curative?

NO

Patient willing?

NO

Combination therapies

Data from RNS System may identify surgical candidates

Resective Surgery or Ablation

RNS System

VNS Therapy

NO
Deep Brain Stimulation (DBS)

- FDA approved as adjunctive therapy in individuals 18 years of age or older with drug resistant partial onset seizures.
- In clinical trials, 17 percent greater reduction in the average number of seizures per month.
Other options

**KETOGENIC DIET**
4 fats: 1 protein + carbohydrates
Unsure mechanism of action, goal is state of ketosis
Usually started in the hospital, need dietitian
Benefit seen over period of several months to years.

**EPIDIOLEX**
FDA approved [CBD] oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy, in patients 2 years of age and older.
- Lennox-Gastaut syndrome and
- Dravet syndrome

https://www.epidiolex.com/
Patient & Family Resources

American Academy of Neurology

American Epilepsy Society

Epilepsy Foundation Kentuckiana

International League Against Epilepsy
Thank you