What's New in Epilepsy Treatment?

Treatment Options for Drug-Resistant Epilepsy

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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.

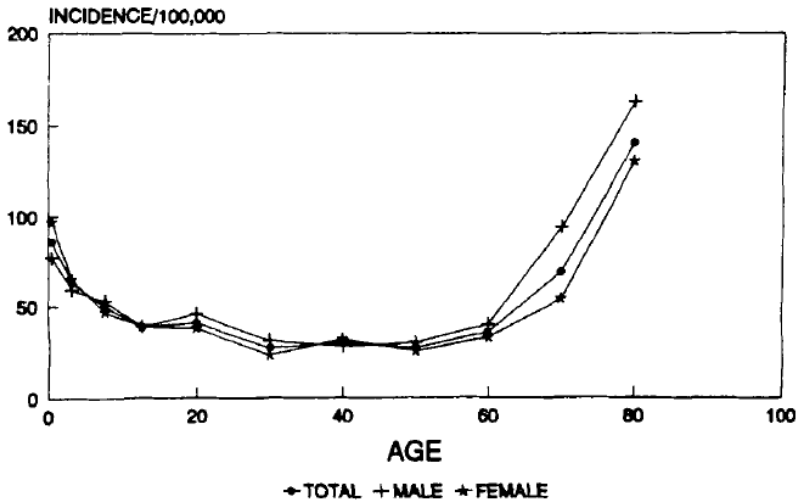
ILAE Official Report, 2014

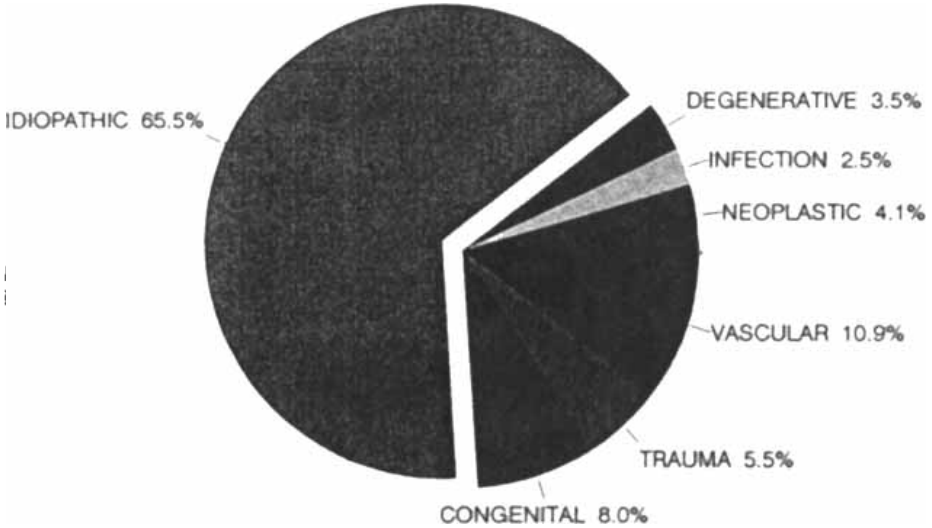
Incidence and Prevalence

- 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.

Epilepsy Foundation

Incidence and Prevalence





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

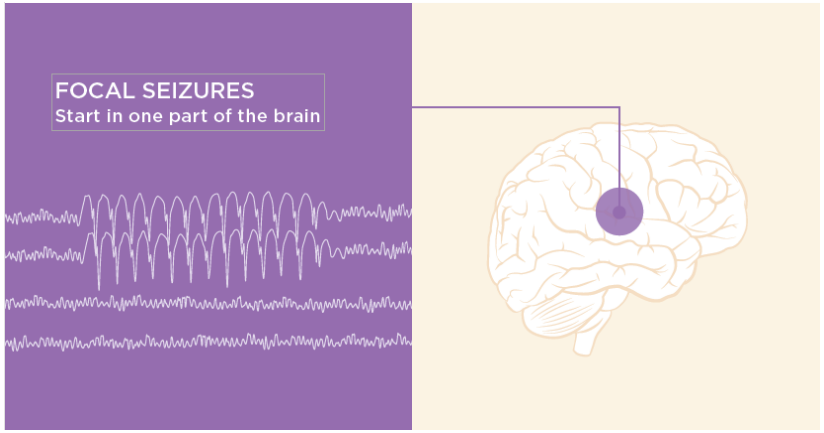
- Etiologies

Hauser et al, 1992

Morbidity and mortality

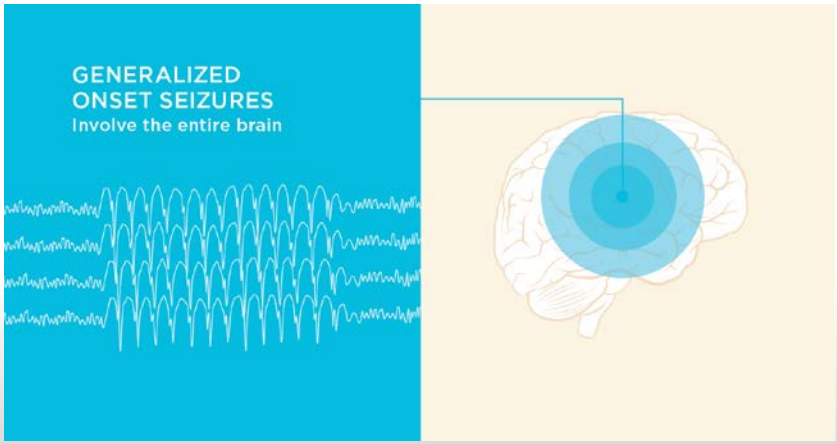
- Seizure related
  - Accidents
- Other
  - Headache
  - Sleep disturbance
  - AED side effects
  - Memory loss
  - Psychiatric (Depression, anxiety, ADHD)
  - Endocrine (hormonal changes)
- SUDEP (Sudden unexpected death in Epilepsy)
  - Refractory epilepsy
  - Highest risk in first 2 years
  - Risk 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

Wyllie's Treatment of Epilepsy, 2015

What is Drug-Resistant Epilepsy

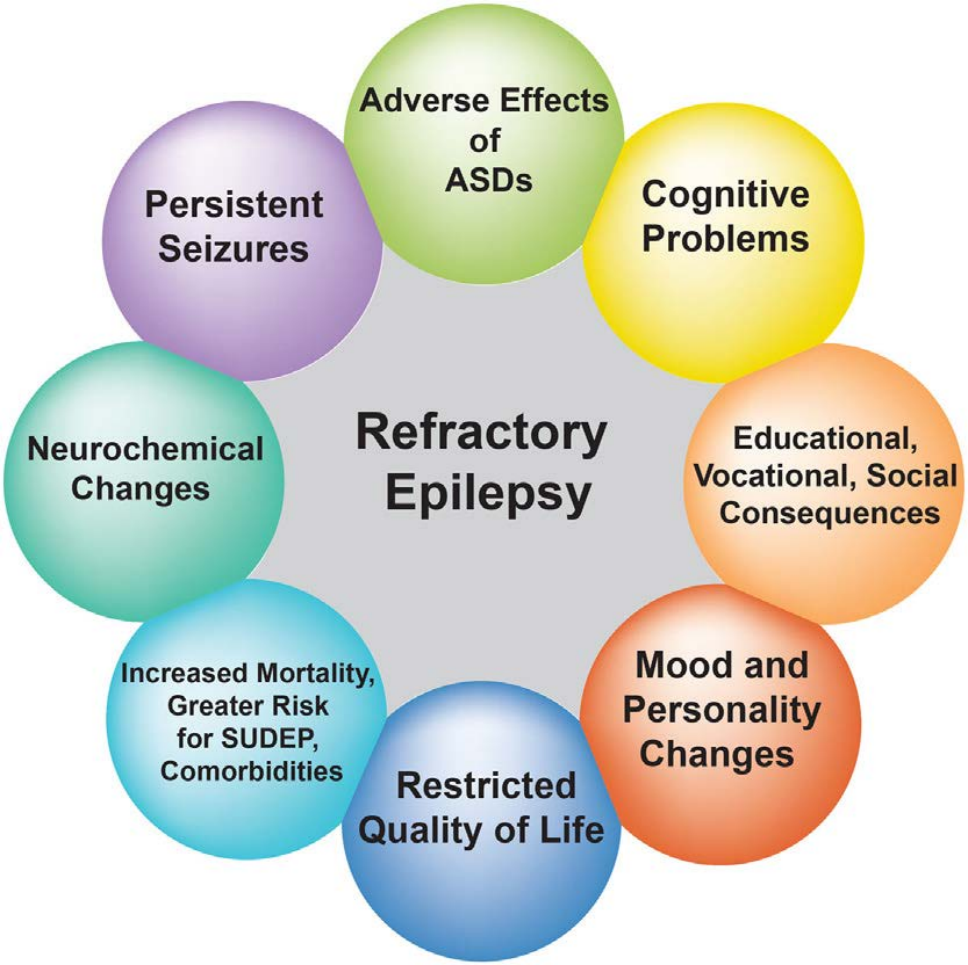
If you've tried 2 anti-seizure medications and still have seizures, you may have drug-resistant epilepsy.

<5% Success Rate

After trying 2 medications, the chance that a 3rd medication will control seizures is <5%.[2]

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

Impact on Quality of life



Tang F et al, 2018

SPECIAL ARTICLE

Quality improvement in neurology: AAN epilepsy quality measures

Report of the Quality Measurement and Reporting Subcommittee of the American Academy of Neurology

- 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

DBS

VNS/RNS

ANTIEPILEPTIC DRUGS

BRAIN SURGERY

KETOGENIC DIET

Facts and misconceptions

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

Adapted from Vakharia VN et al, 2018

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.

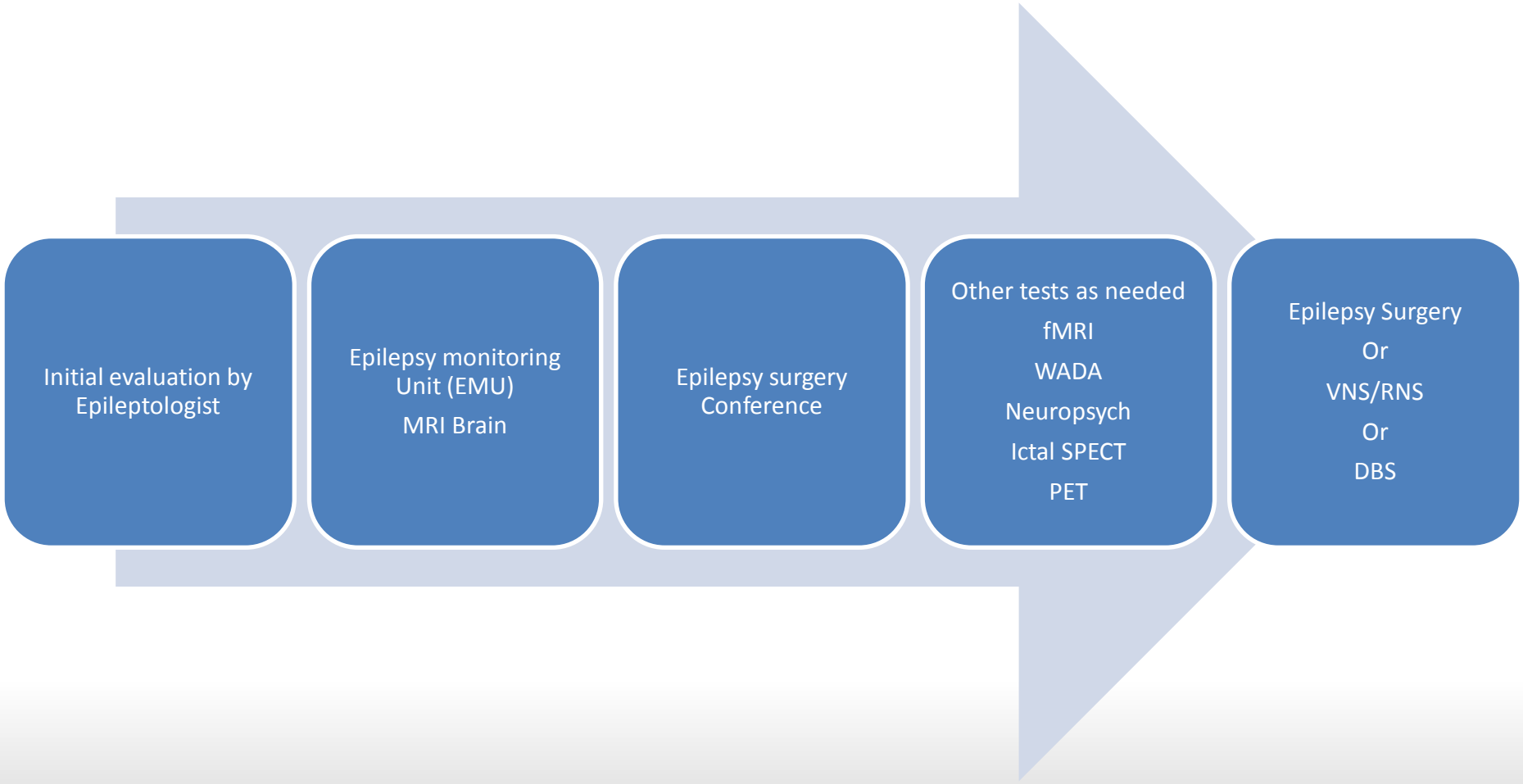
Epilepsy Monitoring Unit (EMU)

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

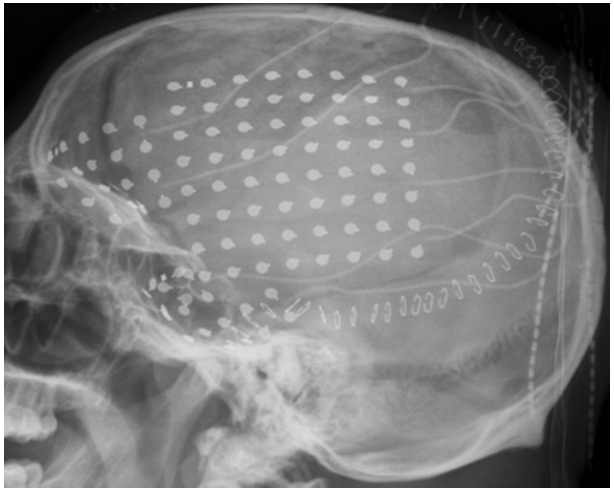
CEC workflow

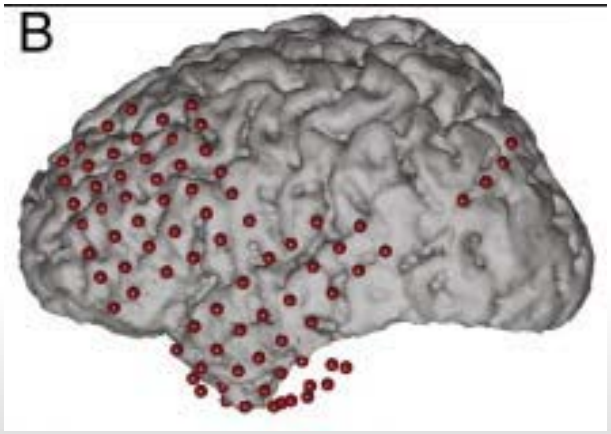


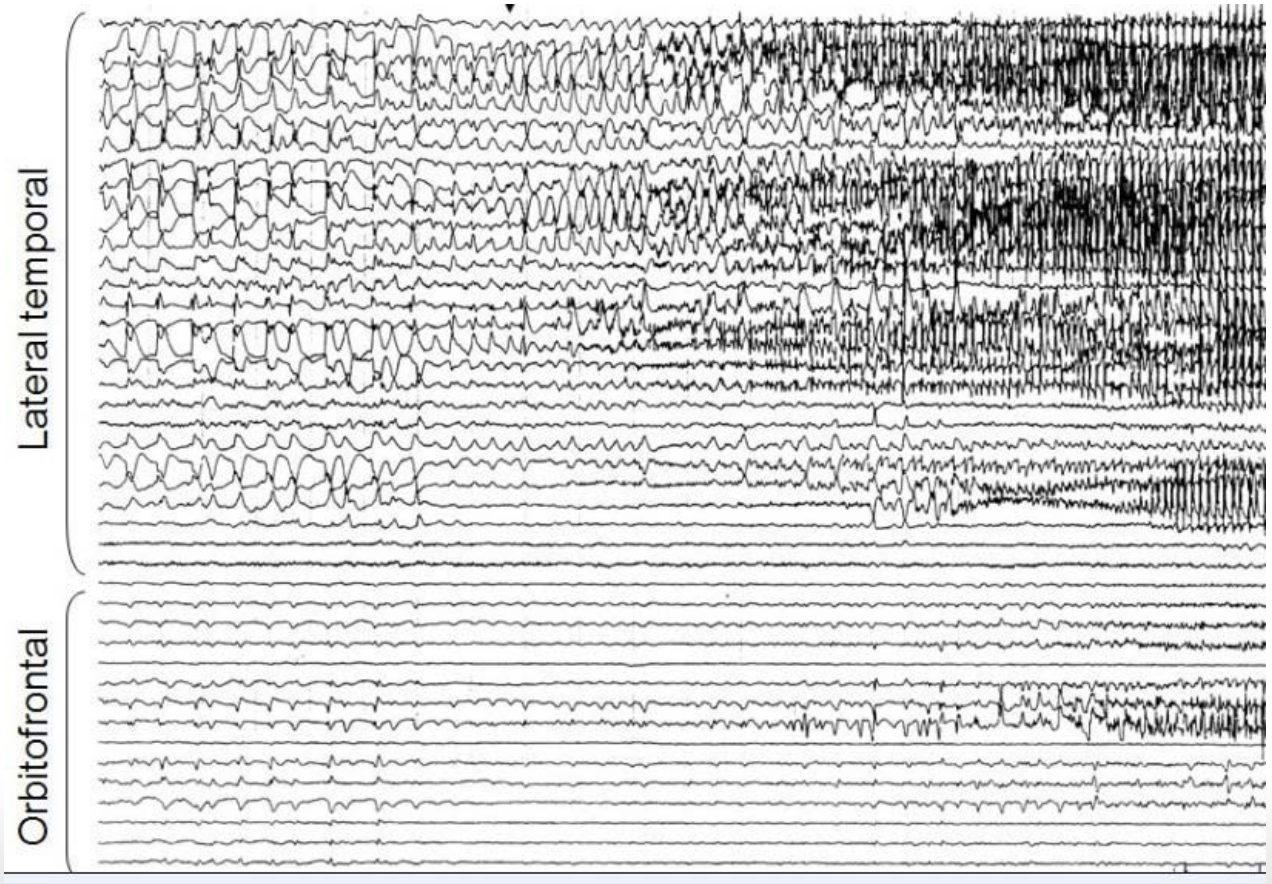
Pre-surgical work up

- 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

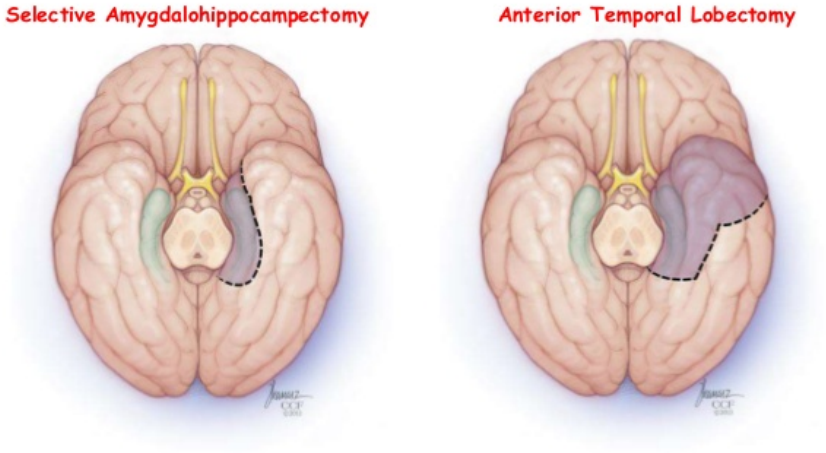
- Laser Interstitial Thermal Therapy (LITT)

~20% can discontinue drugs post-op

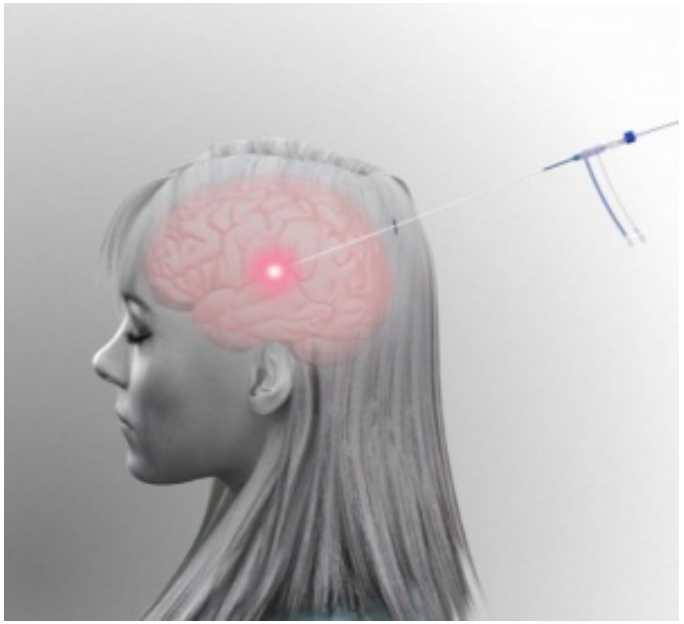
Wyllie's Treatment of Epilepsy, 2015

Epilepsy Surgery

Temporal Lobectomy



Laser therapy



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

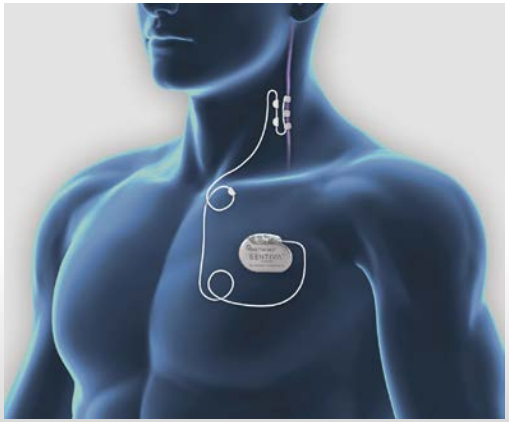
Seizure freedom with surgery

- 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%

Wyllie's Treatment of Epilepsy, 2015

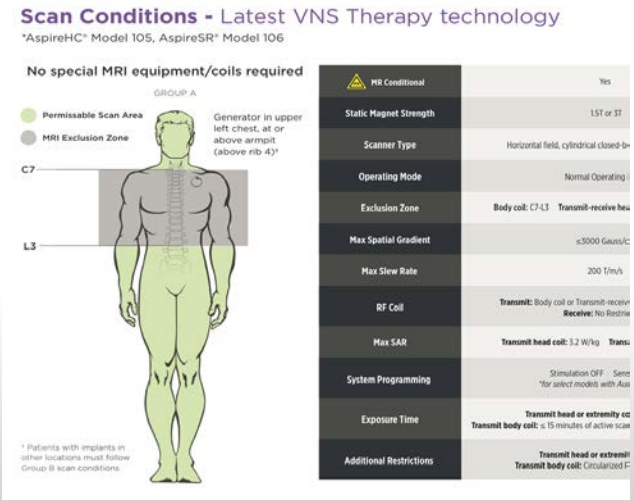
VNS- Who's a good candidate?

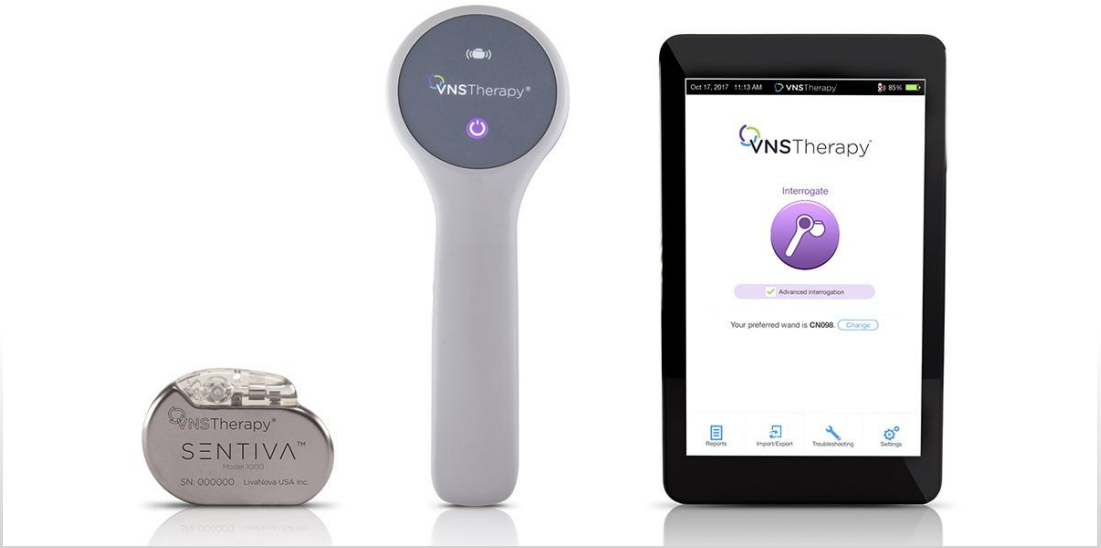
- Drug-resistant focal epilepsy where surgical resection of the focus is not possible (Seizures unlocalizable or multifocal)
- Drug-resistant generalized epilepsy (not FDA approved indication)
- Electrodes are surgically implanted around the left vagus nerve and connected to the pulse generator in the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

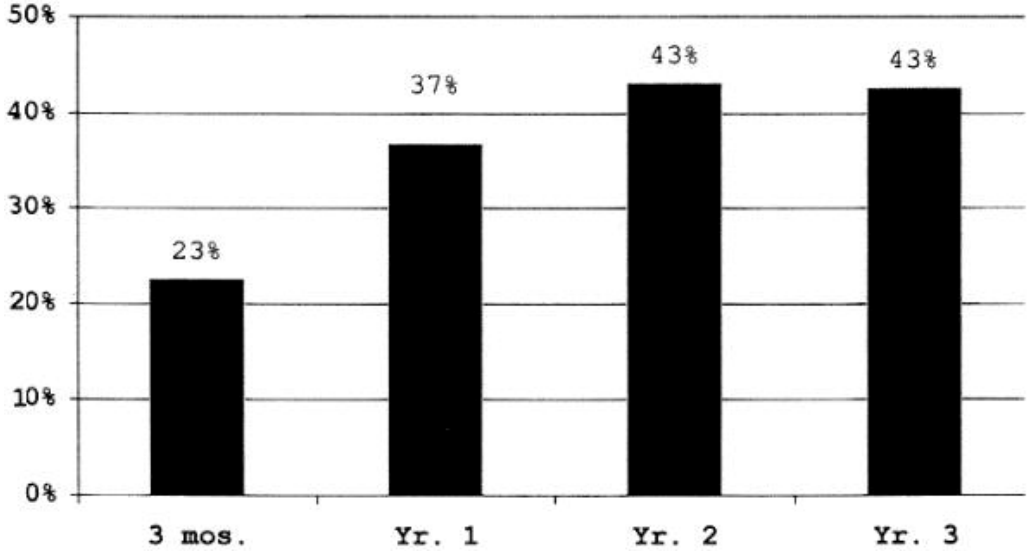




https://us.livanova.cyberonics.com/patient-resources

Seizure outcomes with VNS

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



Patients experiencing a >=50% seizure frequency reduction

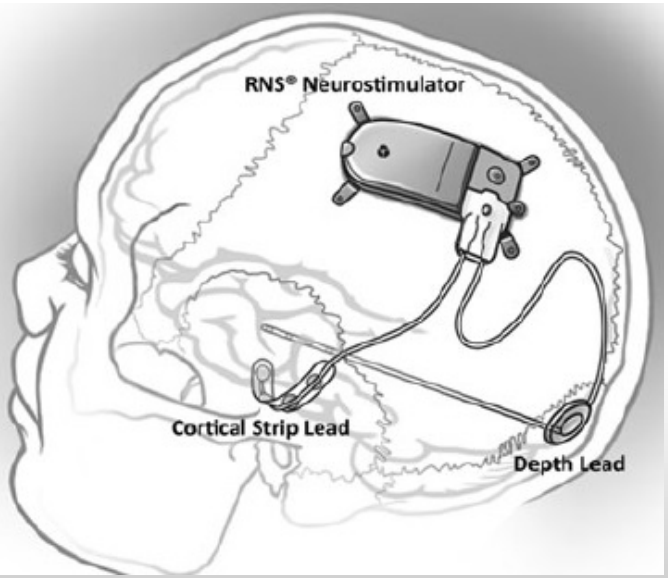
- Improved quality of life (improvements in alertness, attention, memory and concentration)
- Reduced SUDEP rates

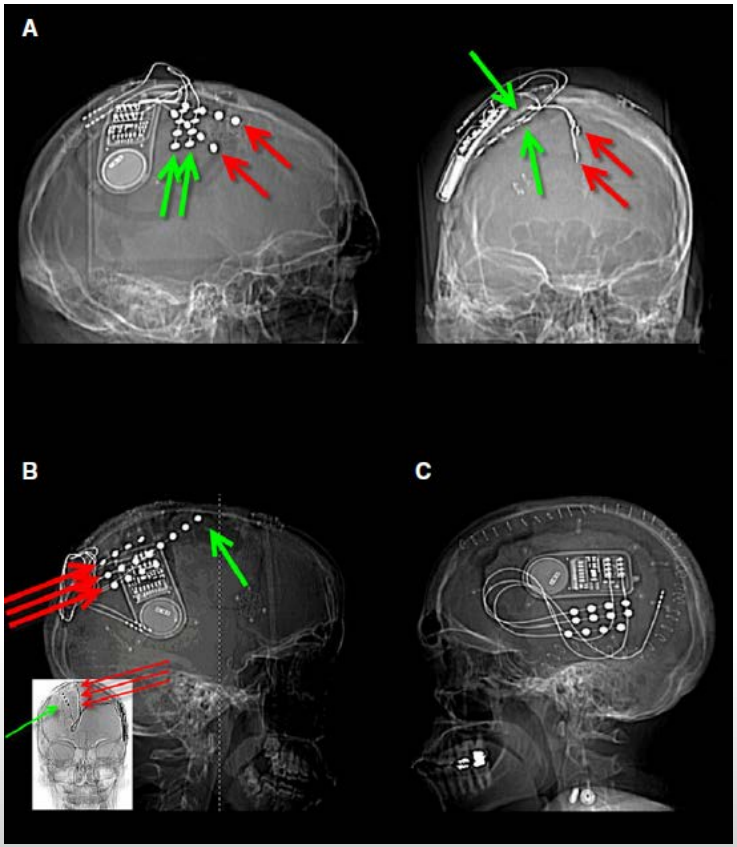
The Vagus Nerve Stimulation Group, 1995
Morris and Mueller, 199

Neuropace (RNS)

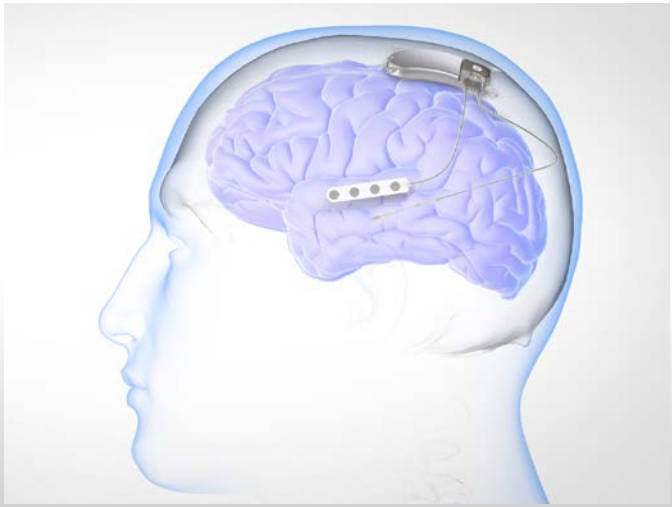
Who is a good candidate?

- 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





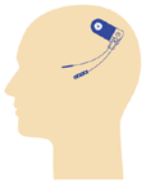
RNS System Placement Procedure



- 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.

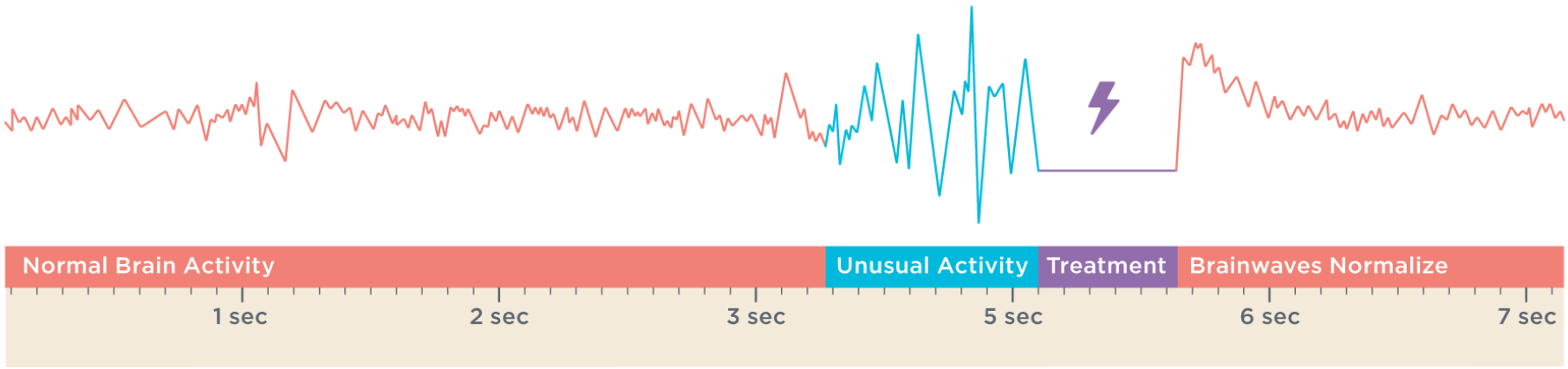
REMOTE MONITOR AND WAND

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



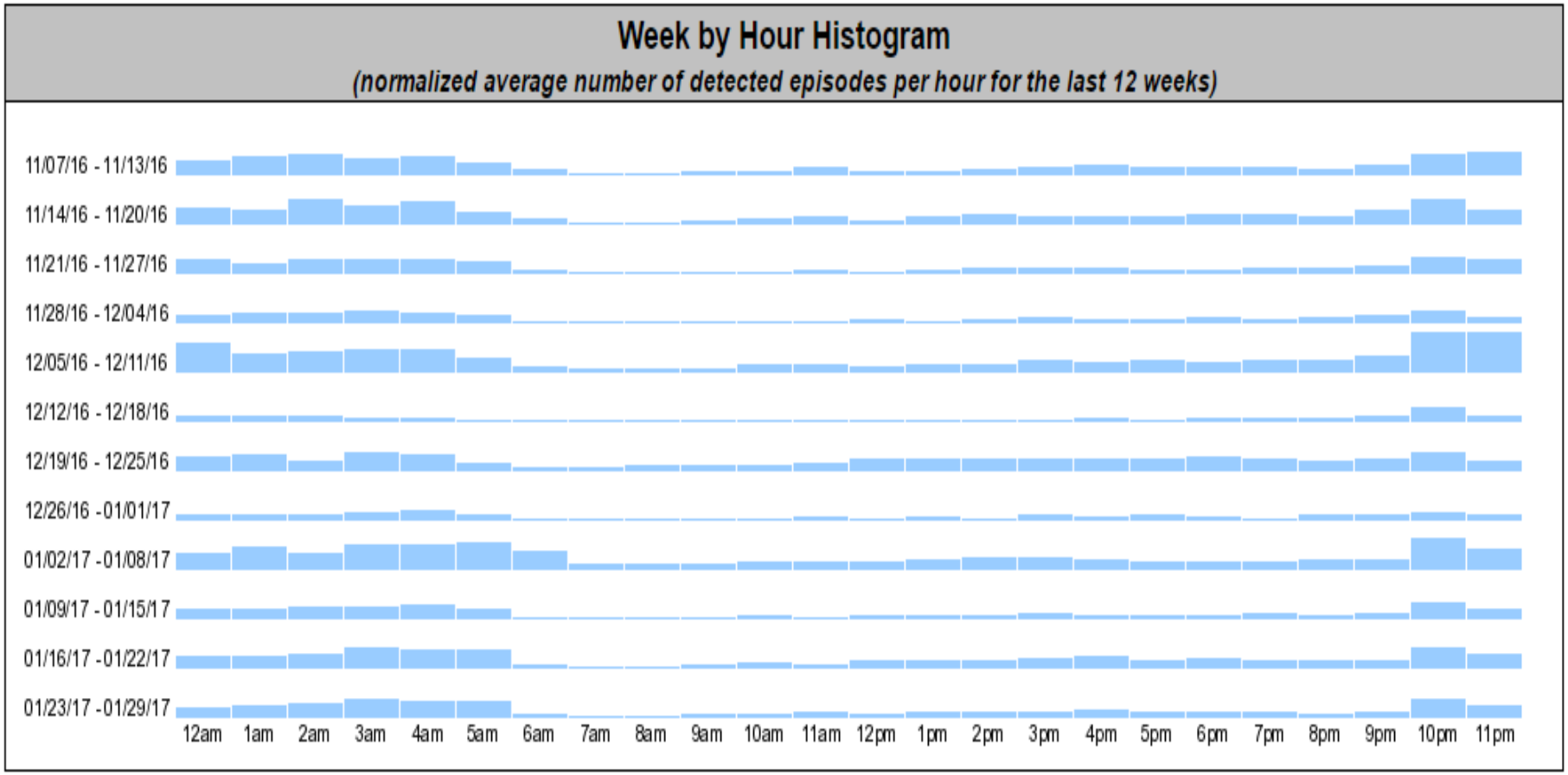
Monitors your brain activity twenty-four seven

Detects unusual activity that can lead to a seizure

Responds with a small electrical pulse to prevent a seizure from occuring

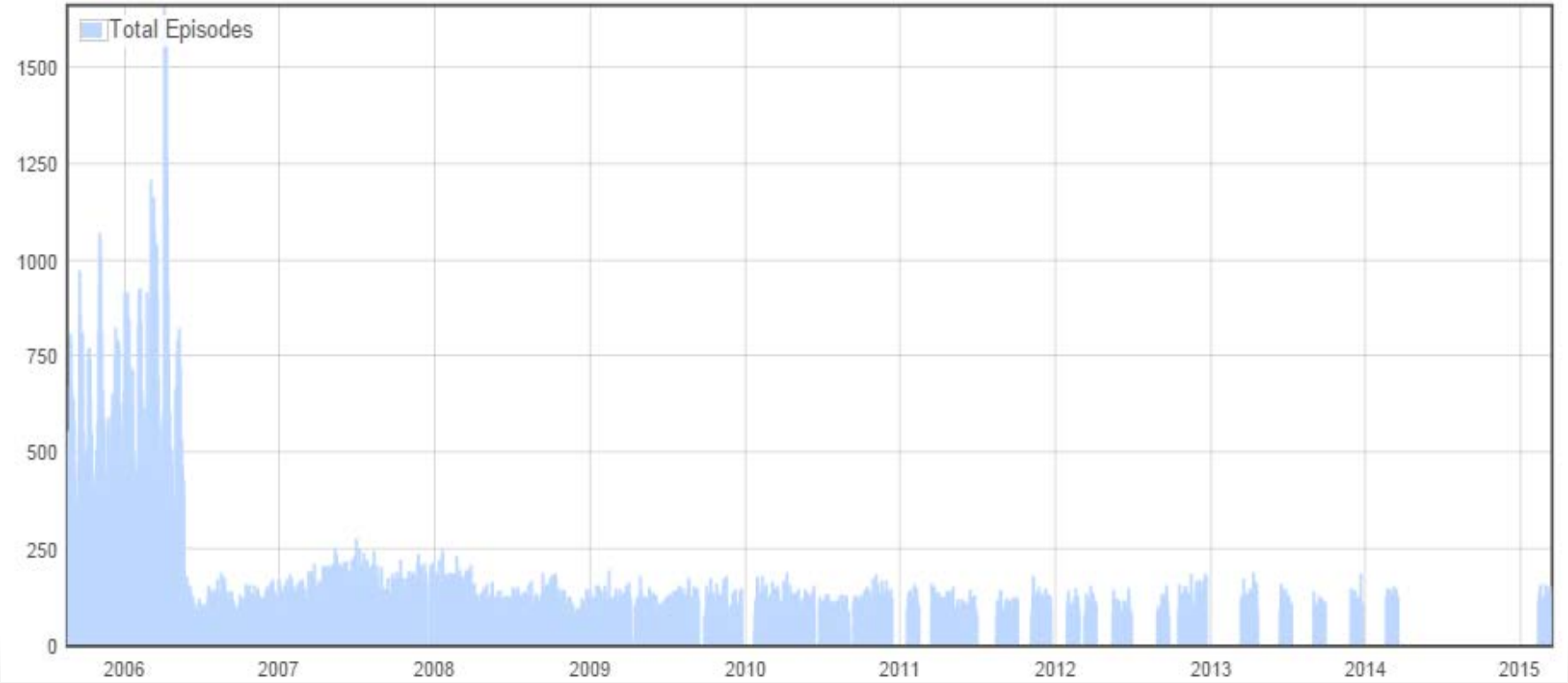
RNS- Circadian Patterns

Histogram data demonstrate nocturnal changes in cortical excitability.



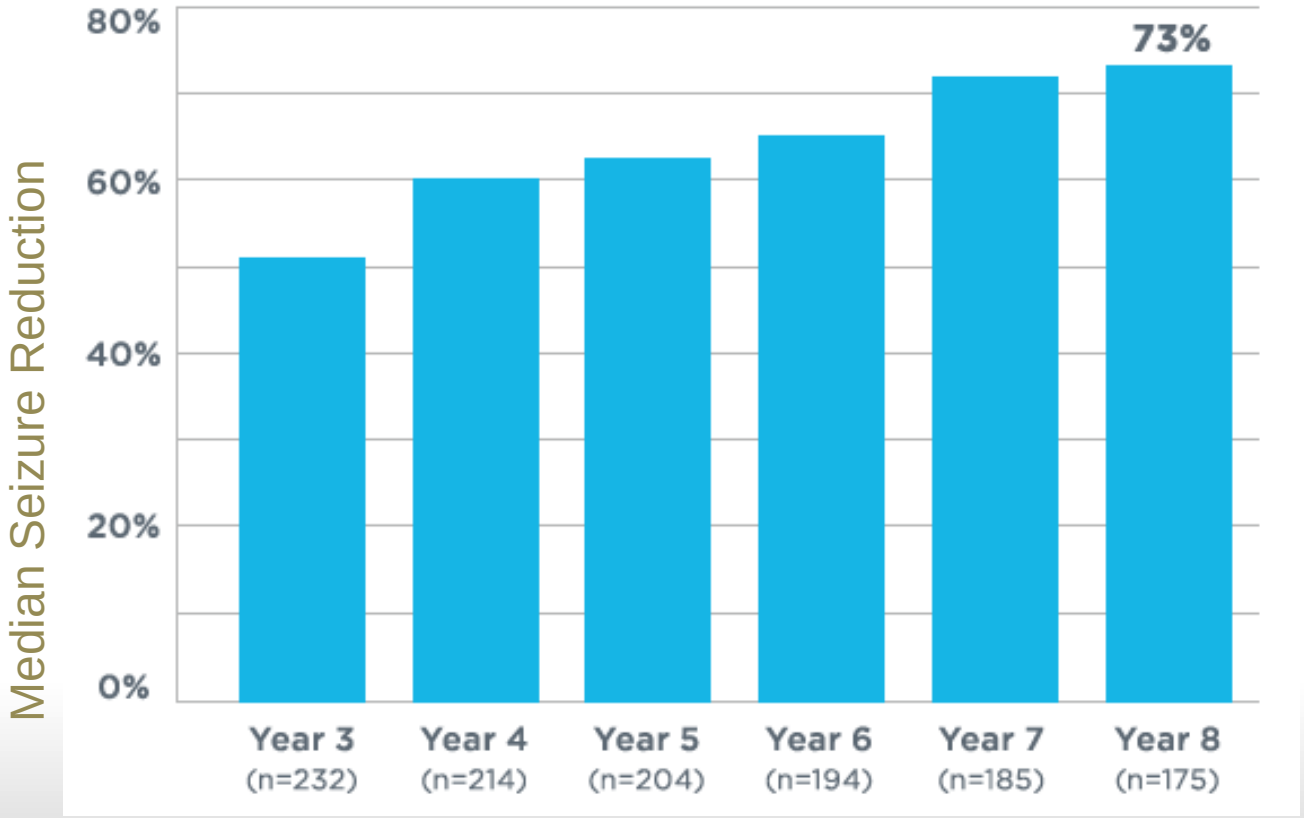
Assess Effects of Medication

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

Meador KJ, et al. Epilepsy Behav, 2015. Morrell et al. American Epilepsy Society. December 2016.

Neuromodulation Devices for Epilepsy

These therapies for drug-resistant epilepsy work differently.

Where stimulation is delivered

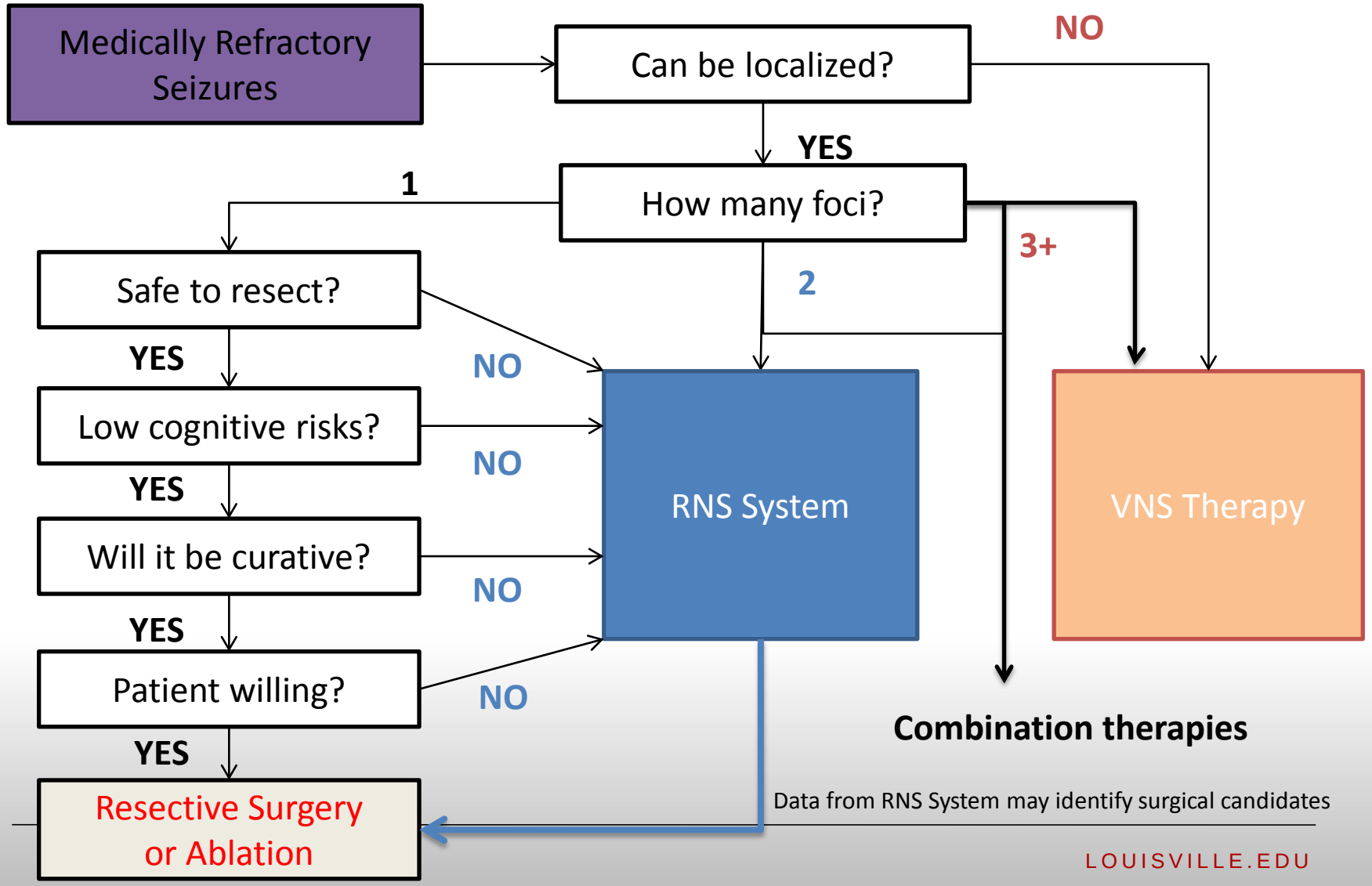
When stimulation is delivered

Amount of stimulation delivered

Stimulation side effects

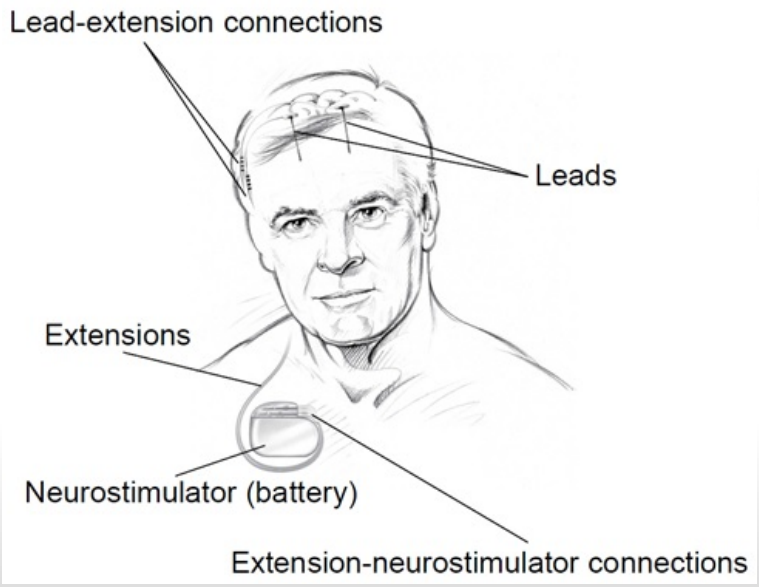
1. Cyberonics, Vagus Nerve Stimulation System Manual 2. Heck, CN, 2014

Defining the care pathway



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

ILAE International League Against Epilepsy

Thank you