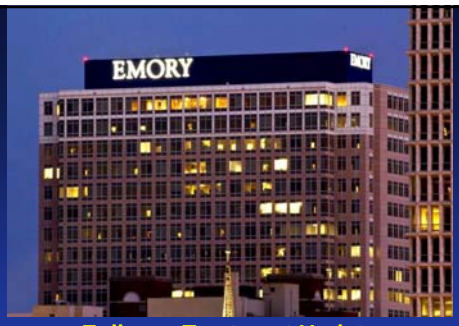
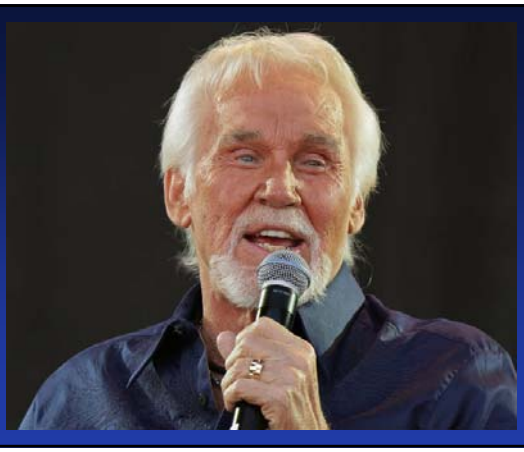


Epilepsy Treatment Update

Edward Faught, M.D.
Professor of Neurology
Director, Emory Epilepsy Program

Conflicts of Interest

- Consultant: Biogen (antiinflammatories), Eisai (perampanel), UCB (levetiracetam, lacosamide, brivaracetam)
- Data-Safety Monitoring Boards: SAGE (allopregnanolone), SK Life Science (cenobamate)
- Research support: UCB, Eisai, Brain Sentinel, NIH
- First author of pivotal trial reports: topiramate, felbamate, zonisamide, carisbamate



Kenny Rogers' Treatment Principles

You've got know when to hold 'em

Know when to fold 'em

Know when to walk away

Know when to run

--"*The Gambler*"

I. Know when to hold 'em: If it ain't broke don't fix it

II. Know when to fold 'em: This drug ain't working!

III. Know when to walk away: None of these drugs is working!

IV. Know when to run: Status epilepticus

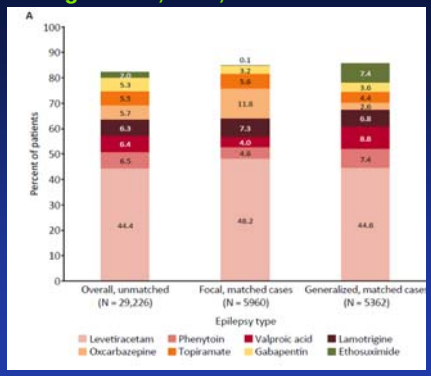
When to get a seat at the AED poker table: Medicate after the first seizure?

- Current practice- NO, if normal exam, normal scan, normal EEG, no remote history of neurological disease.
- Newer information- you need to think about the effect on quality of life should a second seizure occur, especially tonic-clonic- more people should start medications than in current practice*

*Bao E et al. Antiepileptic drug treatment after an unprovoked first seizure: A decision analysis. *Neurology* 2018: 9:91(15): e1429-1439

- **HAVING A SECOND SEIZURE IS BAD NEWS**
- Physical risk, SUDEP risk
- Social and employment harm
- Driving restriction
- Dread degrades quality of life
- Seizures may beget seizures

First drug choice, USA,2015-17



Faught E, Helmers S, Kim H, Thurman D, Kalilani L. Epilepsy and Behavior, 2018

Play to win: Adequate dosing is important

- "Start low, go slow"- maybe, but don't stay there
- "Titrate to effect"- OK if seizures are frequent and not severe- NOT OK otherwise
- Target dose- Pick a MIDRANGE dose and go for it, especially if GTC, first seizure or infrequent seizures

Examples: Levetiracetam- 2000 mg/day
Oxcarbazepine- 1200 mg/day
Lamotrigine- 400 mg/day
Topiramate-400 mg/day
Lacosamide-400 mg/day

Why not titrate to the "lowest effective" dose? Rule of thumb

It takes 5 times the average interseizure interval to evaluate the effectiveness of an ASM

- Daily seizures: you know in a week, so you can "titrate to effect"
- Yearly seizures: 5 years, so pick an adequate midrange dose, you can't titrate to effect!

I. Know when to hold 'em: If it ain't broke don't fix it

- Example: Patient is irritable on 2000 mg/day levetiracetam. You decide to switch to oxcarbazepine and give patient a switchover schedule, goal is1200 mg/day OXC monotherapy.
- . Returns in 2 months, taking 1000 mg LEV and 600 mg OXC, reports not seizures, not irritable, feels fine
- Don't push ahead with your plan. You have succeeded! Leave it alone!

But be sure it ain't broke

- **?Unrecognized seizures**
- What does your family say?
- Do you wake up with a bitten tongue?

- **Unrecognized side effects**
- Dizziness, ataxia, blurry vision= easy
- Irritability, anger, depression, fatigue
- = hard, you have to probe

II. Know when to fold 'em: the "Decision Point Dose"

- Is this drug doing **any good at all?**
- Most AEDs, if they are going to work, work at low to medium doses, at least in part
- If absolutely no benefit at a certain dose for each drug, **FOLD 'EM!** (toss it out).
- Examples of possible decision point doses:
  - CBZ 600mg, OXC 1200 mg
  - LEV 2000 mg
  - LTG, TPM, LCM 400 mg

Play your cards: Do something!

- Any change in therapy after a seizure (dose, medication) extended the time to next hospital or ED encounter for seizures, compared to no change in therapy.

Faught E, Helmers S, Begley C, Thurman D et al. New AEDs and other factors affecting hospital admission. *Epilepsy and Behavior* 2015

There is no such thing as a "breakthrough seizure"- Either the drug/dose is not working or it is not being taken.

What's in the deck?

New medications

Antiseizure Medications

(ASMs)

Antiepileptic Drugs (AEDs) don't yet exist, but they may soon- drugs to prevent the development of epilepsy

Newer Medications

Medications for focal/tonic-clonic seizures

Perampanel (Fycompa)- glutamate blocker (unique)

- Brivaracetam (Briviact)- son of levetiracetam
- Eslicarbazepine (Aptiom)- grandson of carbamazepine

Special purpose drugs

- Cannabadiol- Lennox Gastaut, Dravet syndromes
- Stiripentol (Diacomit)- Dravet synidrome
- Clobazam (Onfi)- for LGS but is broad spectrum benzodiazepine
- Everolimus- for tuberous sclerosis related seizures
- Rescue benzodiazepines

Perampanel (Fycompa): Glutamate blocker (kainate type)

- Advantages: qD dosing, good cognitive profile, good vs GTC, does not seem to worsen myoclonus or absence, unique mechanism of action
- Disadvantages: Irritability in some, frequent dizziness and somnolence at onset
- Start : 2 mg hs. Target: 6-8 mg hs

Brivaracetam (Briviact): Synaptic release inhibitor

- Advantages: Starting dose is effective dose, narrow titration range. Irritability may be less likely than with levetiracetam.
- Disadvantages: Irritability is still possible
- Start: 50 mg BID. Target: 100 mg BID

Eslicarbazepine (Aptiom): Sodium channel blocker

- Advantages: qD dosing. Lesser drug interactions than carbamazepine. Possibly lower risk of hyponatremia
- Disadvantages: Not clearly more efficacious than oxcarbazepine.

Clobazam (Onfi): GABAergic benzodiazepine

- Advantages: less sedating and less likely to induce tolerance than other benzodiazepines. Broad spectrum drug vs. many seizure types
- Disadvantages: Only approved in US for Lennox-Gastaut syndrome. Still some sedative effect
- Start; 10 mg bid Target: 20 mg bid

Rescue benzodiazepines: 2018

- Military- diazepam 10 mg autoinjector
- Rectal diazepam (Diastat)
- Noncommercial preparations: Buccal midazolam

1st Brigade, 3rd Infantry Division, Kuwait/Iraq border, November 2005

Intranasal Midazolam (Nayzolam) A "rescue" medication

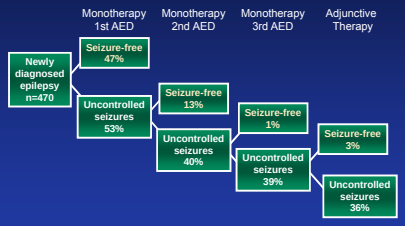
- Advantages: quick onset 5-15 min. Prefilled atomizer. Does not need refrigeration. Has an effect for several hours.
- Disadvantages: Shorter acting than lorazepam, likely to be expensive.
- Dose: 5 mg. May repeat in 10 min once.

The Magic Bullet?

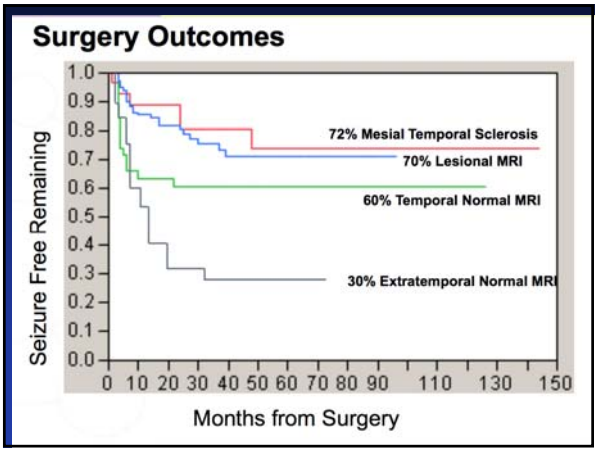
III. Know when to walk away
Referral for surgery:

- Play the odds: after 3 drugs, chance of perfect seizure control is <5%, so walk away from this futile drug game
- If seizures can be localized, chance of perfect seizure control is 50-70%

Efficacy of AEDs- retrospective series, all drugs all seizure types



Kwan P Brodie M et al. N Engl J Med. 2000;342(5):314-319.



Delay in Referral for Surgery

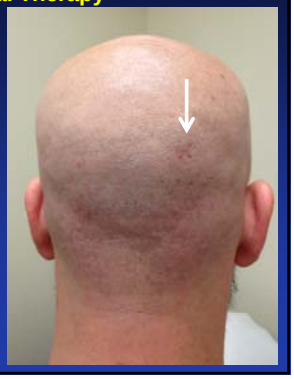
- Diagnosis to referral to UAB Epilepsy Center, 1988:
  16.2 yrs
- Diagnosis to referral to UAB Epilepsy Center, 2002:
  14.1 yrs
- ***Why?- physicians***
  Control is just around the corner
  Occasional seizures aren't too bad
  You can always try one more drug (we have 15)

Why?- patients
Brain surgery is scary!

What patients imagine

Reality 2019
Laser Interstitial Thermal Therapy

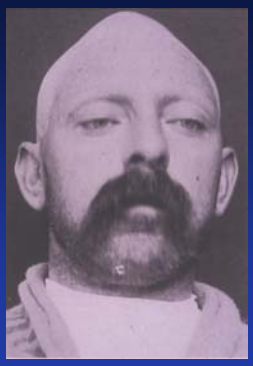
- Does not always require intracranial monitoring
- Home in one day
- Memory outcomes are better
- Seizure free rate for MTS is 60% (70% for open resection)



How to discuss surgery for epilepsy

- Bring it up as a possibility at the time of diagnosis, along with medications and electronic neurostimulator!
- Consider it seriously after 3 drug failures at good doses- BE REALISTIC!
- Emphasize that newer techniques often require smaller operations and are likely safer: LASER is sometimes the magic word!

The Surgical Question: Where is the Seizure Focus?



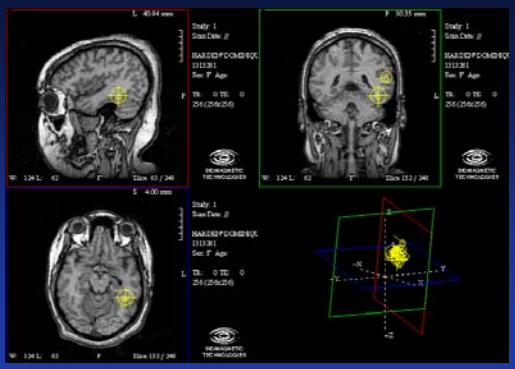
Harvey Cushing's first tumor patient

Meningioma 1895

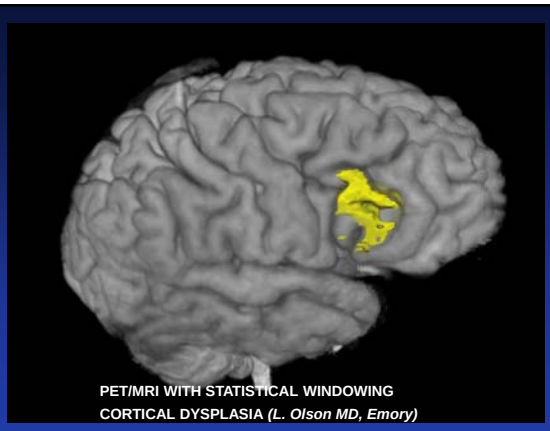
Magnetoencephalography

Thanks to Jeff Killen, UAB

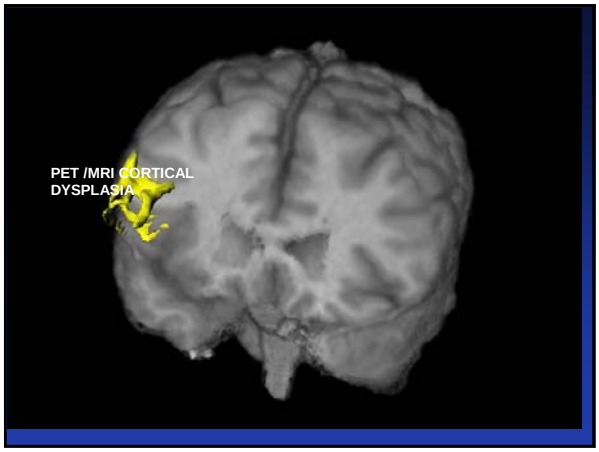
Magnetoencephalogram

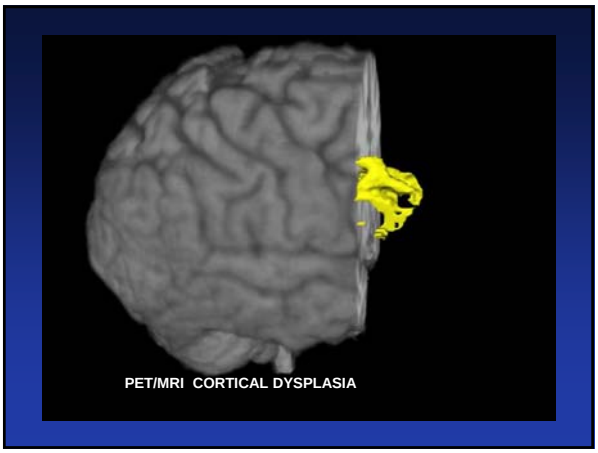


MAGNETIC SOURCE IMAGING



PET/MRI WITH STATISTICAL WINDOWING
CORTICAL DYSPLASIA *(L. Olson MD, Emory)*

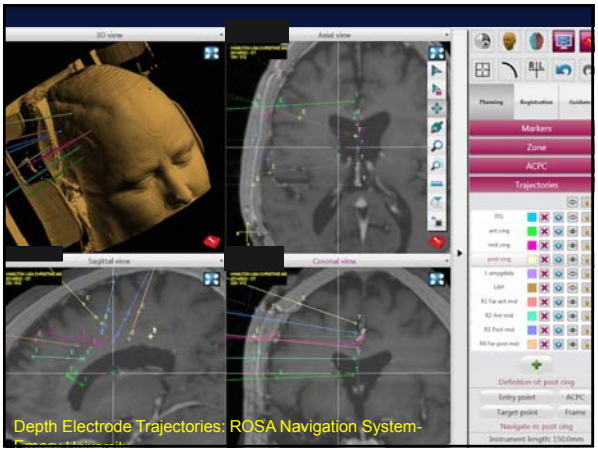




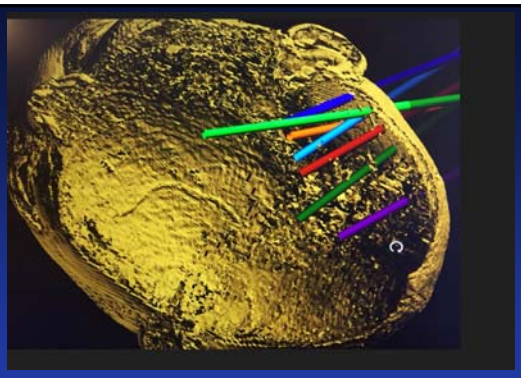
PET/MRI CORTICAL DYSPLASIA

Stereo EEG

- The cortex is 3-dimensional
- Multiple depth electrodes are often better than subdural grids and strips for visualizing this
- Modern depth electrodes are relatively safe- 1-2% risk of hemorrhage, and are much more comfortable than a craniotomy for the patient
- Surgical robots now allow very precise placement of depth electrodes
- 90% of intracranial EEG at Emory is now stereaeo-EEG instead of subdural recording



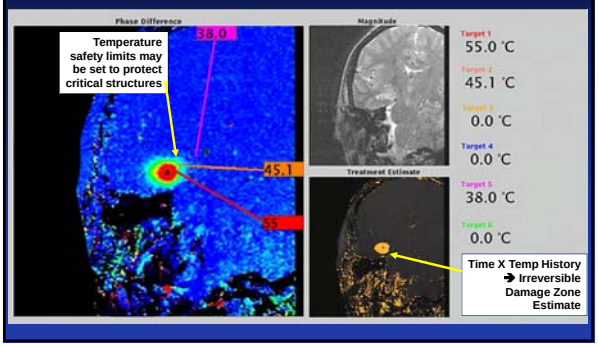
Depth Electrode Trajectories: ROSA Navigation System-



Depth Electrode Trajectories

ROSA surgical navigation system, Emory University Hospital

Workstation: Near Real-time MRI to 1) Estimate Irreversible Damage Zone 2) Protect Critical Structures

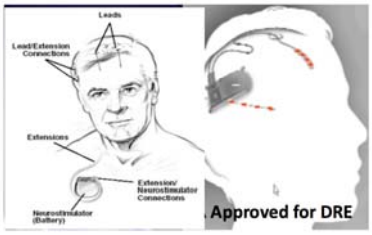


Neurostimulation

- Vagal nerve stimulator- consider after 2 or 3 drugs if not proceeding toward surgery,
- Responsive neurostimulator- electrodes in or on brain, tune to EEG seizure onset. Best for areas not safe to resect, or 2 separate foci (e.g. bitemporal independent seizures)
- Deep brain stimulation- anterior nucleus of thalamus, bilateral. If there is no clue where the seizures originate, or for intractable generalized seizures

Devices for Epilepsy

SANTE	RNS
Medtronic Inc	NeuroPace Inc



Approved for DRE

5 years SANTE
- 69% Sz Reduction
- 68% Resp. Rate
- 16% w/ 6 mon. of Sz freedom
- Improved QOL

7 years RNS
- 66% Sz Reduction
- 56% Resp. Rate
- 13% had >1 yr Sz freedom
- Improved QOL

IV: Know when to run:

New dosing recommendations for convulsive status epilepticus

EMORY HEALTHCARE

Management of Status Epilepticus

(For Adults and Children > 40 Kg)

Emory University, Emory University Midtown, Emory Saint Joseph's, Emory Johns Creek

1st, 2nd and 3rd line management is based on the ILAE 2016 guidelines for Generalized Convulsive SE, which is defined as bilateral convulsive seizure activity for ≥ 5 minutes or ≥ 2 seizures without return to consciousness.

This document is intended to be a general guideline and should not supersede clinical judgment.

Date Reviewed/Revised: 7/2018
Approved by Critical Care Executive Committee 7/2018; Formulary & Stewardship Committee 9/2018
Approved by Pharmacy & Therapeutics Committee: EUH, EUHM, SJH, EJCH 9-10/2018

Goals of Treatment:
1. Safe and timely cessation of both clinical & electrographic seizure activity while maintaining airway, breathing, & circulation
2. Identification and treatment of underlying seizure etiology
3. Long-term maintenance of seizure control

Developed by Hiba Haider, MD, PhD, Emory Epilepsy Program, Department of Neurology, Emory University

First Line Treatment: 0-5 minutes

- Lorazepam 4 mg IV
- Midazolam 10 mg IM
- Start second line treatment simultaneously!

Second Line Treatment- 5-30 minutes: IV Over 15 Minutes.

- Levetiracetam 50 mg/kg. (e.g. 3000 mg)
- or
- Fosphenytoin 20 mg PE/kg. (e.g. 1500 mg)
- or
- Valproate 40 mg/kg (e.g. 3000 mg)
- or
- Lacosamide 400 mg

Third Line Treatment: 1 hour +

- Midazolam 0.2 mg/kg IV load (e.g 15 mg)
- Propofol 2 mg/kg IV load (e.g. 150 mg)

–CONTINUOUS EEG

The future of epilepsy care

- True ANTIEPILEPTIC drugs- prevent development of epilepsy. ?After serious head trauma, intracranial bleeds, complex febrile seizures, other high-risk situations.
- Gene therapy- correct ion channelopathies or other specific pathophysiology
- Tuned neurostimulation- local or remote

- *Will destroying brain tissue someday be considered barbaric?*