

# **EPILEPSY ESSENTIALS FOR PRIMARY CARE**

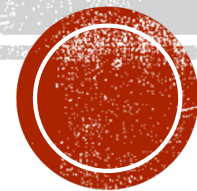
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# OUTLINE

- Work up of new-onset event
- Management of established patients
- Guidelines to choose anti-seizure medications
- Stopping/switching anti-seizure medications
- Non-pharmacological therapies
- Referring the patient to an epileptologist



# CASE-1

- 18 y.o woman is brought to ED by family for 2 witnessed seizures. Seizures are described as convulsions with tongue bite. While being triaged, she had another seizure which is described as tonic-clonic seizure per nurse
- Parents say she has been staying up late to finish a project. Rest of the history is noncontributory.
- EEG and MRI are normal.
- Does he have epilepsy ?
  - A. Yes
  - B. No
  - C. Need more information



# DEFINITIONS

- **Epileptic seizure**
  - International League Against Epilepsy (ILAE) has defined seizure as “a transient occurrence of sign and/or symptoms due to abnormal excessive and synchronous neuronal activity in brain”
- **Acute Provoked Seizure**
  - Occurs in the context of an acute brain insult or systemic disorder, such as, but not limited to, stroke, head trauma, a toxic or metabolic insult, or an intracranial infection
- **Unprovoked Seizure**
  - A seizure that occurs in the absence of an acute provoking event





# SOME CAUSES OF PROVOKED SEIZURES

## Neurologic

- Head Trauma/Brain surgery
- CNS infection
- CNS tumor
- Cerebrovascular disease
- Cerebral hypoxia/ischemia

## Medications

- Toxicity / overdose
- Withdrawal

## Drugs and Alcohol

Acute use of cocaine, methaqualone, and stimulants

Withdrawal from alcohol and benzodiazepines

## Metabolic and Electrolyte Imbalances

Sodium

Calcium

Magnesium

Glucose

Urea nitrogen



# WHAT IS EPILEPSY

- At least 2 or more unprovoked seizures on separate days, generally >24 hours apart
- One unprovoked seizure and a 60% probability of further seizures over next 10 years
- Diagnosis of epilepsy syndrome



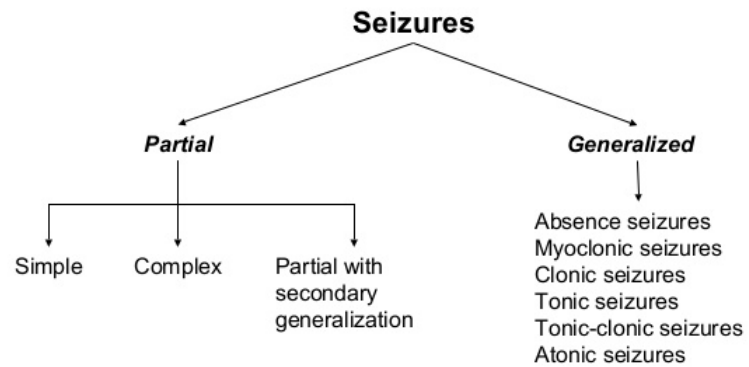
# EPILEPSY AS A CONCEPT

- The “disease” known as epilepsy does not mean the presence of seizures
- Rather, it means that the brain has, for whatever reason, developed a state in which a seizure could happen
- A person can be at no immediate risk of a seizure and still suffer from epilepsy (eg: person who is on an effective antiepileptic medication)
- In other words, epilepsy is brain hyperexcitability with or without acute seizures



# OLD CLASSIFICATION

## CLASSIFICATION OF SEIZURE



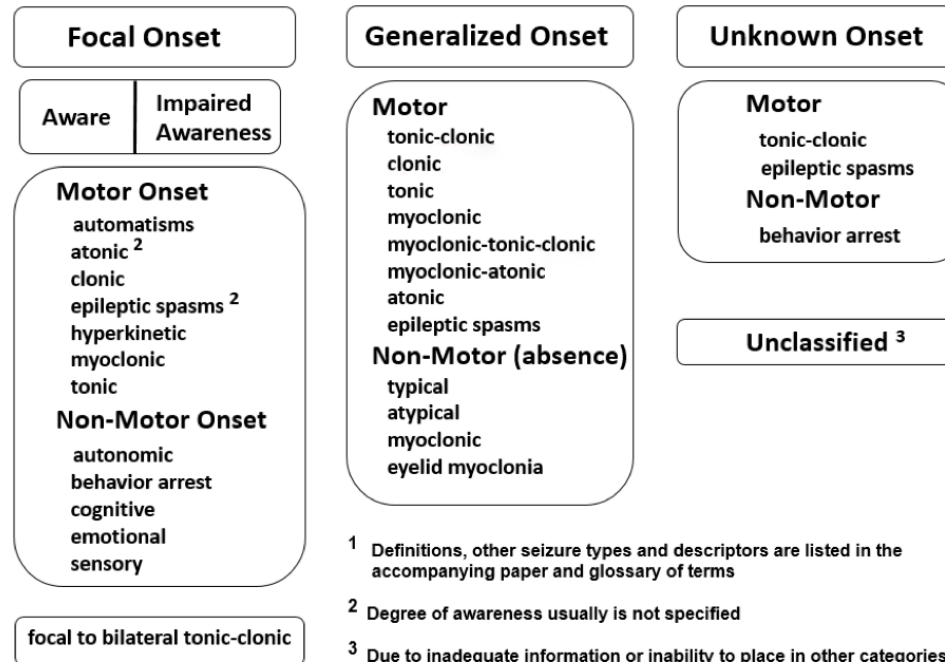
\* ILAE classification of seizures 1981

Epilepsia 22: 489-501



# NEW CLASSIFICATION

## ILAE 2017 Classification of Seizure Types Expanded Version <sup>1</sup>



<sup>1</sup> Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms

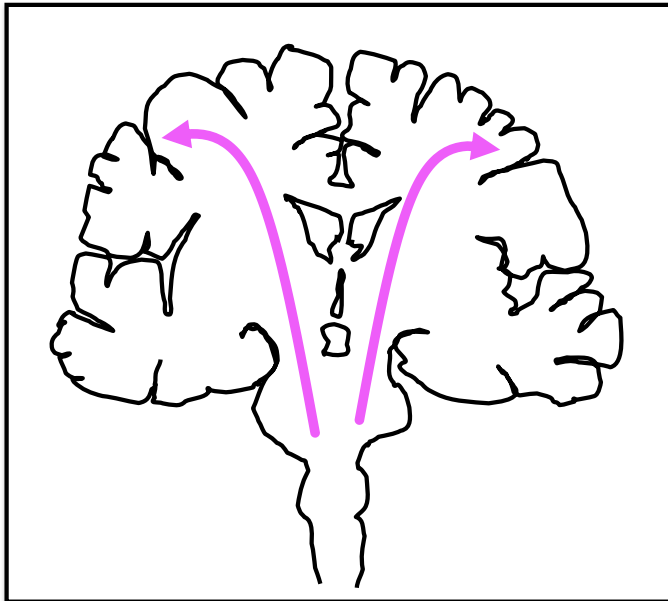
<sup>2</sup> Degree of awareness usually is not specified

<sup>3</sup> Due to inadequate information or inability to place in other categories



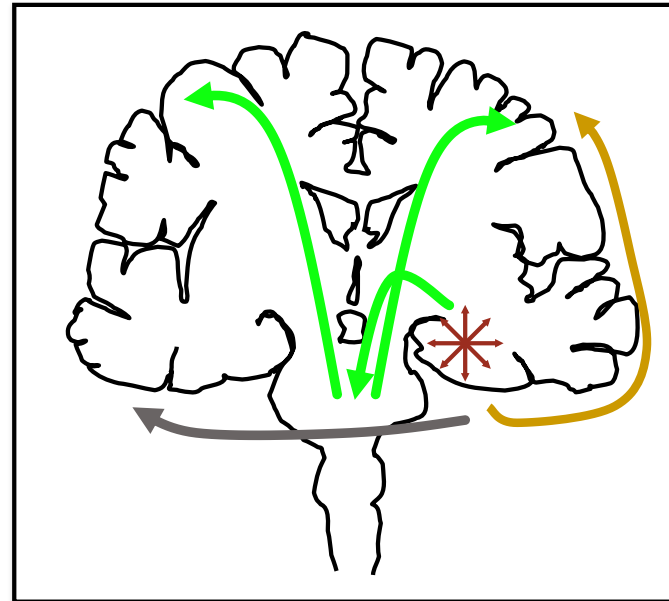
## Generalized Onset

Absence, Myoclonic,  
Tonic, Clonic,  
Tonic-clonic, Atonic



## Focal Onset

Retained awareness (Simple partial)  
With loss of awareness (Complex partial)  
Evolution to bilateral convulsive seizures



Courtesy Dr. Imerman

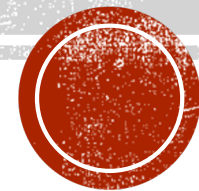


# THE NEW ONSET SEIZURE

- Confirmation that the events ARE seizures
- What kind of seizure?
- Determine the etiology
- Risk of recurrence
- Selection of treatment



# ARE THE EVENT'S SEIZURES?





# DIFFERENTIAL DIAGNOSES: PHYSIOLOGIC

- Syncope
  - Cardiac (Arrhythmia)
  - Non-Cardiac Syncope (Vasovagal, Dysautonomic)
- Metabolic (Hypoglycemia)
- Migraine
- Sleep Disorders (Narcolepsy, REM sleep behavior disorder, Periodic Limb Movements of Sleep, Parasomnias)
- Movement Disorders (Paroxysmal Dyskinesia)
- Transient Ischemic Attacks

# DIFFERENTIAL DIAGNOSES: PSYCHOLOGIC

- Psychogenic Non-Epileptic Events
- Malingering
- Panic Attacks/Anxiety
- Intermittent Explosive Disorder
- Breath-holding Spells



**“DIAGNOSIS OF SEIZURES AND EPILEPSY LARGELY  
BASED UPON THE HISTORY”**



# SEIZURE-SPECIFIC HISTORY

- Context of event(s)
  - Circumstances under which the events occur
  - Timing – sleep, wakefulness
  - Position (lying, sitting, standing, transitions)
  - Triggering factors (sleep deprivation, illness, etc)
- Detailed description of all event(s) “From start to finish”
  - Any warning ahead of time?
  - What was the sequence of signs/symptoms?
  - Duration of event (frequency)?
  - Post event signs/symptoms – Confusion, headache
  - Vocalization, tongue bite, incontinence
- Any witnesses?
- Prior similar or dissimilar events?



# OTHER RELEVANT HISTORY

- **Known risk factors**
  - Pre/peri/post-natal complications
  - Head trauma
  - CNS infections
  - Other medical conditions
- **Developmental level**
- **Medications/toxin exposures**
- **Family history**
  - Febrile seizures or epilepsy, 1<sup>st</sup> and 2<sup>nd</sup> degree relatives



# VIDEO 1



# VIDEO-2



## **Epileptic Seizure**

- Initial cry, followed by tonic and later clonic phase
- Head turn, face twitching
- Eyes usually open
- Rhythmic, synchronous movements
- Lateral tongue bite
- Start-Stop
- Average seizure duration is less than 2 minutes

## **Nonepileptic Event**

- Vocalization not always first
- Back arching, pelvic thrusting, head no-no movements
- Eyes usually closed
- Semi-rhythmic, asynchronous movement
- Cheek bite or tip of tongue bite
- Waxing and waning (start-stop-start-stop)
- Variable duration





## VIDEO-3: FOCAL SEIZURE WITH IMPAIRED AWARENESS



# WHEN TO ORDER AN EEG

- After the first seizure
- Seizures poorly controlled, increasing in number, changing in type
- Considering discontinuing AED medication
- Patient admitted to hospital for seizures
- Patient in ER, has/just had seizures and fails to awaken
- After status epilepticus especially if patient fails to awaken



# ROLE OF BRAIN IMAGING

- In adults/children who have their first seizure, a neuroimaging scan of the brain should be obtained.
- MRI Brain is the best study for imaging the epileptic brain
- Typically do not need contrast
  - Contrast can be used if infection/inflammation/malignancy is suspected
- When to order an MRI Brain:
  - Initial evaluation unless certain primary generalized epilepsy
  - Repeat MRI indicated if change in seizure type or frequency
  - Medically intractable epilepsy



# TO TREAT OR NOT TO TREAT



# TREATMENT OF 1<sup>ST</sup> SEIZURE

- Whether to treat the first seizure remains controversial:
  - If no risk factors with normal MRI, risk of recurrence is around 30% in 2 years
- ASMs often cause adverse reactions and side effects in up to 1/3 of patients treated long-term
  - Very young children and elderly are at increased risk for adverse drug effects
- Quality of life issues also influence decision to treat the first seizure
  - Possible lifestyle restrictions (e.g. on driving, working), likelihood of medication compliance, cultural and social issues



# RISK FACTORS FOR SEIZURE RECURRENCE

<b>Risk Factor</b>	<b>Relative increase in risk</b>
Epileptiform features on EEG	Threefold
Symptomatic seizure (cause determined)	Twofold
Patient asleep at time of initial seizure	Twofold
Partial seizures	Slight increase
Family history of seizures or epilepsy	Slight increase



# WHICH ANTI-SEIZURE MEDICATION?





# GOALS OF TREATMENT

- Seizure control without side effects
- Monotherapy much preferred
- Easy-to-use regimen
- Optimal quality of life

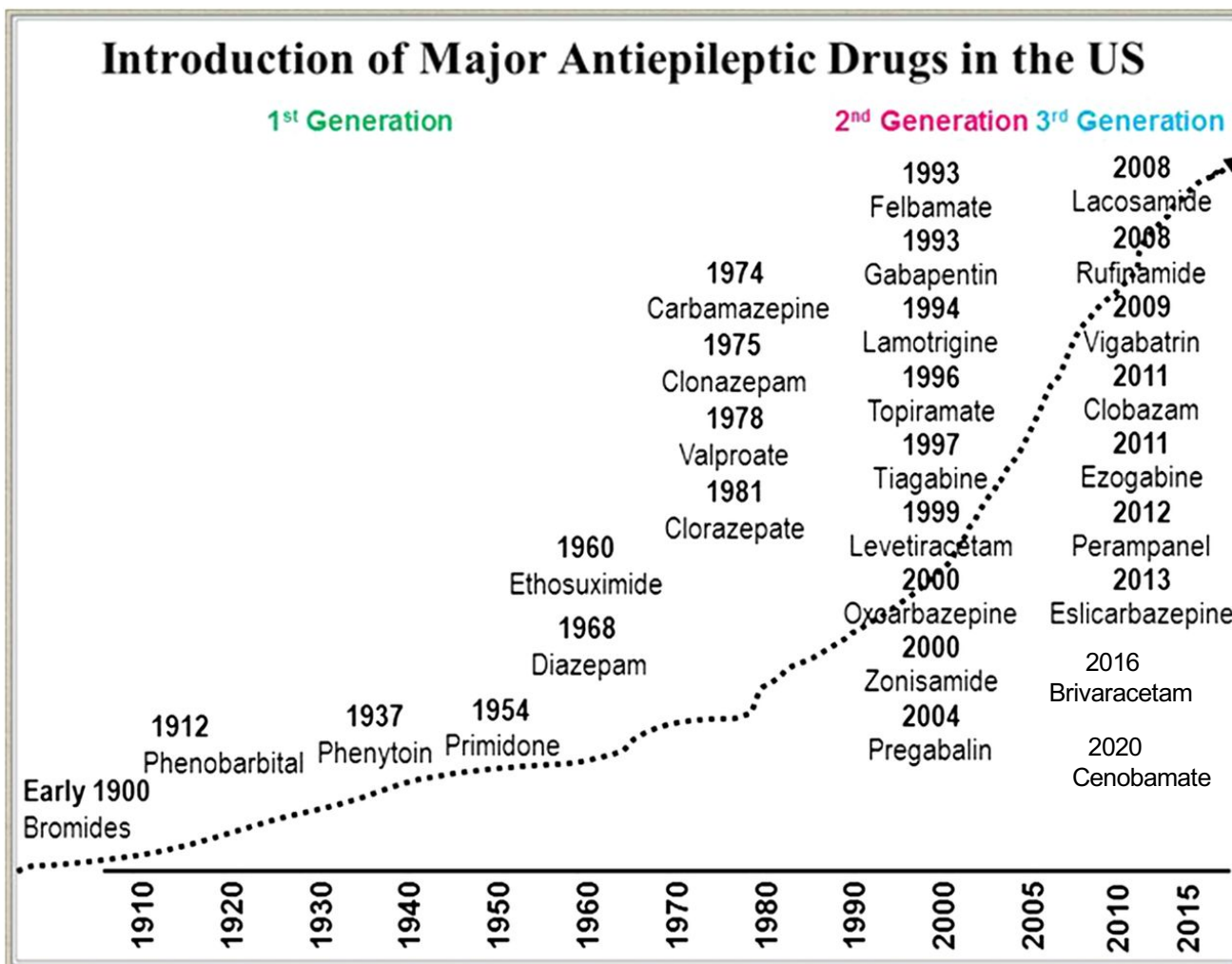




# Introduction of Major Antiepileptic Drugs in the US

1<sup>st</sup> Generation

2<sup>nd</sup> Generation 3<sup>rd</sup> Generation



# TARGET FOR ASM

- Increase inhibitory neurotransmitters – **GABA**
- Decrease excitatory neurotransmitters – **Glutamate**
- Block voltage-gated inward positive currents – **Na, Ca channels**
- Increase outward positive current – **K channels**
- Many ASMs are pleotropic – act via multiple mechanisms



# MECHANISMS OF ACTION

<b>Fast Na</b>	phenytoin, carbamazepine, oxcarbazepine, lamotrigine, valproate, topiramate, zonisamide, rufinamide
<b>Slow Na</b>	lacosamide
<b>Ca T type</b>	ethosuximide, valproate, zonisamide
<b>Ca voltage gated</b>	gabapentin, pregabalin
<b>K</b>	ezogabine, retigabine
<b>GABA</b>	valproate, phenobarb, benzodiazepines, tiagabine, vigabatrin, felbamate, topiramate
<b>Glu</b>	felbamate, lamotrigine, topiramate, perampanel
<b>SV2</b>	levetiracetam, brivaracetam



# CHOICES TAILORED TO PATIENTS

## CONCOMITANT MIGRAINE

VALPROATE  
GABAPENTIN  
TOPIRAMATE

## ONCE DAILY DOSE

PHENYTOIN  
ZONISAMIDE  
VALPROATE  
PHENOBARBITAL

## AVOID IN YOUNG WOMEN

VALPROATE	higher teratogenic risk
PHENYTOIN	cosmetic effects, hirsutism

## WEIGHT LOSS

TOPIRAMATE  
ZONISAMIDE

## EXTENDED RELEASE

Lamotirgine  
Levetiracetam  
Carbamazepine  
Oxcarbazepine

## MANAGEMENT OF CLUSTER SEIZURES

LORAZEPAM PERORALLY	0.03-0.05mg/Kg
RECTAL DIAZEPAM GEL	0.2-0.5mg/Kg

## HEPATIC ENZYME INDUCERS

PHENYTOIN  
CARBAMAZEPINE (also autoinduction)  
BARBITURATES  
OXCARBAZEPINE  
TOPIRAMATE (weak)

## PARENTERAL AVAILABLE

PHENYTOIN/FOSPHENYTOIN  
VALPROATE  
BARBITURATES  
BENZODIAZEPINES  
Levetiracetam  
Lacosamide

## MAINLY RENAL EXCRETED

GABAPENTIN  
LEVETIRACETAM  
TOPIRAMATE (lesser extend)



# HEPATIC ENZYME INDUCER/INHIBITOR

## Inducer

- Phenobarbital
- Dilantin
- Carbamazepine
- Oxcarbazepine/Eslicarbazepine
- Perampanel
- Ethosuximide
- Topiramate (>200 mg dose)

## Inhibitor

- Valproate



# MANAGEMENT OF ESTABLISHED PATIENTS



# THE ESTABLISHED DIAGNOSIS (?)

- Confirm diagnosis and etiology
- Current and past ASMs (and why they were stopped)
- Are events controlled? – current frequency of events
- Any adverse effects from drugs?
- ASM levels



# SEARCH FOR CAUSE OF POORLY CONTROLLED SEIZURES

- Are some, or all, seizures nonepileptic?
- Have/are wrong drugs used for the types of seizures or epilepsy syndrome?
- Has polypharmacy contributed to poor control and increased side effects?
- Underlying structural cortical lesion needing removal?





# THERAPEUTIC RANGE OF ASM

- A guide, not a goal
  - Always obtain trough levels to establish baseline
  - Hard to rely upon limited data, broad range, individual differences
- Value of serum ASM levels?
  - Provide initial target range in patients with infrequent seizures;
  - Help understand why a patient
    - continues to have seizures (low or changing levels)
    - has side effects, especially with polypharmacy
  - Verify patient drug compliance



## ADVERSE EFFECTS OF ASM – COMMON

- **Common**
  - Sedation, drowsiness, nausea, GI discomfort, incoordination, vertigo, headache, dizziness, blurred vision, ataxia
- **Drug specific:**
  - **Phenytoin:** nystagmus, gingival hyperplasia
  - **Valproic acid:** tremor, weight gain
  - **Levetiracetam:** psych-related issues – e.g., agitation
  - **Acetazolamide, topiramate, zonisamide:** kidney stones
  - **Carbamazepine** and **oxcarbazepine:** hyponatremia
    - Frequency: oxcarbazepine > carbamazepine



# ADVERSE EFFECTS OF ASM – SERIOUS

- **Hypersensitivity reactions**
  - **Lamotrigine**: rash (SJS/TEN) - slow titration
  - **Carbamazepine**: rash - HLA-B\*1502
- **Hepatotoxicity**
  - **Felbamate**: fulminant hepatitis and aplastic anemia (BW)
  - **Valproic acid**: hepatotoxicity
- **Vision**
  - **Vigabatrin**: Permanent vision loss
- **Suicidal ideation**
  - **All ASMs** increase risk of suicidal thoughts/behavior
  - Incidence rate: 0.43% treated patients vs. 0.24% of patients receiving placebo



# ADVERSE EFFECTS OF ASM – OTHERS

- Hematologic effects
  - Thrombocytopenia (**valproic acid**)
  - Aplastic anemia (**felbamate**)
  - Leukopenia (**carbamazepine**)
- Endocrinologic effects
  - Weight gain (**valproic acid, gabapentin, pregabalin**)
  - Weight loss (**topiramate, zonisamide**)
  - Risk of osteoporosis/osteopenia (**old generation ASMs**)
- Teratogenicity
  - Pregnancy category: C or D



# HOW TO MANAGE ADVERSE EFFECTS?

Assess how serious the adverse reaction is, then discontinue current ASM...

- ...when life-threatening conditions occur
  - Steven Johnsons Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)
  - LFT elevations due to valproic acid or felbamate (U.S. boxed warning)
  - Pancreatitis due to valproic acid
- ...when current physical condition may worsen
  - Hyponatremia (Na < 127 meq/L) due to oxcarbazepine
  - Repeating kidney stones, paresthesias due to topiramate, zonisamide
- ...when current AED affects patient's QOL
  - Tremor due to valproic acid



# DISCONTINUING ASM

- Seizure freedom  $\geq 2$  years (adults) and  $\geq 1$  year in children:
  - $>60\%$  chance of successful ASM withdrawal;
- Factors which favor a successful ASM withdrawal:
  - Seizure control achieved easily on one drug at a low dose
  - No previous unsuccessful attempts at AED withdrawal
  - Normal neurologic exam and EEG
  - Primary generalized seizures except JME
- Assess risks/benefits of driving, risk of injury, desire for pregnancy.

Practice parameter. Neurology. 1996;47:600–602.



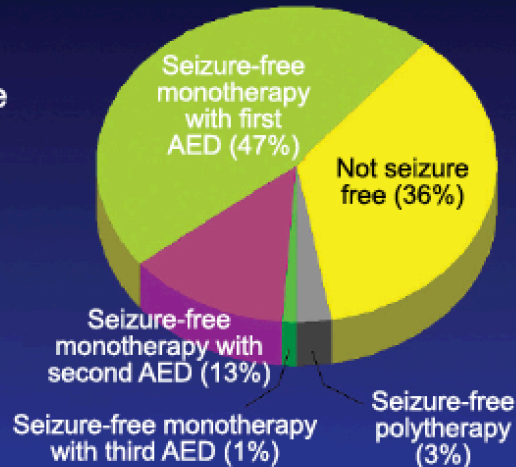
# MEDICALLY INTRACTABLE EPILEPSY:

LIKELIHOOD OF BECOMING SEIZURE-FREE AFTER 3<sup>RD</sup> APPROPRIATE ANTI-SEIZURE MEDICATION 4%

## 63% remained seizure free

Seizure-free rates were similar between those treated with a single older AED (67%) and those treated with a newer AED (69%)

Previously untreated patients  
(n = 470)



- **Medications:** 30-40% of patients continue to have seizures despite optimum medication
- **Video EEG Monitoring:** Any patient who continues to have SZ despite treatment with medications should undergo inpatient video-EEG monitoring: characterize SZs, alter management, epilepsy surgery evaluation and recognize psychogenic seizures or seizures due to other causes (e.g. cardiac).
- **Epilepsy Surgery** = only potential cure for epilepsy:
  - Anyone who fails 2 tolerated medications but continues to have disabling SZs should be referred to a surgical epilepsy center for evaluation
- **Neuromodulation – RNS, DBS, VNS:**
  - Patients with focal onset seizures –RNS/DBS
  - Patients with focal and generalized onset – VNS
  - Consider only for patients who are not surgical candidates
- **Ketogenic /Low Glycemic Index or Modified Atkins Diets:**
  - Only for children, difficult to tolerate or maintain, but effective for medically intractable cases;
  - Modified Atkins diet now being tried in adults with some success.



## WHEN TO REFER TO EPILEPTOLOGIST?

- **Optional:**
  - Don't want to deal with seizures
  - Need help with diagnosing more complicated epilepsy syndromes
  - You have tried all common ASMs and would like other options
  - Patient "requires" multiple ASM and management is complicated.
  - You would like patient to undergo long-term epilepsy monitoring/ambulatory EEG monitoring
- **Mandatory:**
  - Medically intractable epilepsy – consideration of non-pharmacological therapies





# PATIENT EDUCATION

- If miss a dose, take it as soon as possible. If it is almost time for next dose, take only that dose. DO NOT take double up or take extra doses
- Know relevant adverse effects and report to physician
- Take pills with meals
- Report any new medication to physician
- Take medications as scheduled if getting any surgery



# GENERAL RECOMMENDATIONS

- Engage in daily regular weight-bearing physical activity (provided medically safe)
- Maintain balanced diet rich in protein, calcium and vitamin D
- Stop smoking
- Minimize caffeine intake
- Minimize alcohol intake (1 drink per week)
- Take 1000-1500 mg calcium daily (nutrition and supplement)
- Take 1000 IU of vitamin D if taking non-enzyme inducing ASD and take 2000 IU of vitamin D if taking enzyme inducing ASD



# SAFETY IN DAY TO DAY LIFE

- Don't climb ladders, roofs
- Don't' operate heavy machinery – power tools, fork lift
- Only showers, NO baths, keep electric appliances away
- Avoid open flames
- Cook on the back burners, keep knives in drawers
- No unsupervised swimming – life guard or experienced swimmer needed
- Any sport with helmet, ALWAYS use helmet
- Low lying beds, remove harmful objects from bedroom
- Don't workout on machines which don't stop when you stop (eg: treadmill), okay to use stationary bikes
- Wt lifting: limit to 25 lbs



# DRIVING RESTRICTIONS

- Six states have mandatory physician reporting (Pennsylvania, New Jersey, Delaware, California, Nevada and Oregon)
- But the decision is made by DMV
- No mandatory reporting in New Mexico but have to advise patients
- People with epilepsy have legal obligation to report seizures to DMV
- Most states require patients to be seizure-free for 6 months to resume driving (but ranges between 3-12 months)
- NM: 6 months for regular license, 10 years for CDL
- Encourage honesty





**Resources:**

<https://www.epilepsy.com>



