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Epilepsy 101:

Understanding the Basics & Mastering Medications

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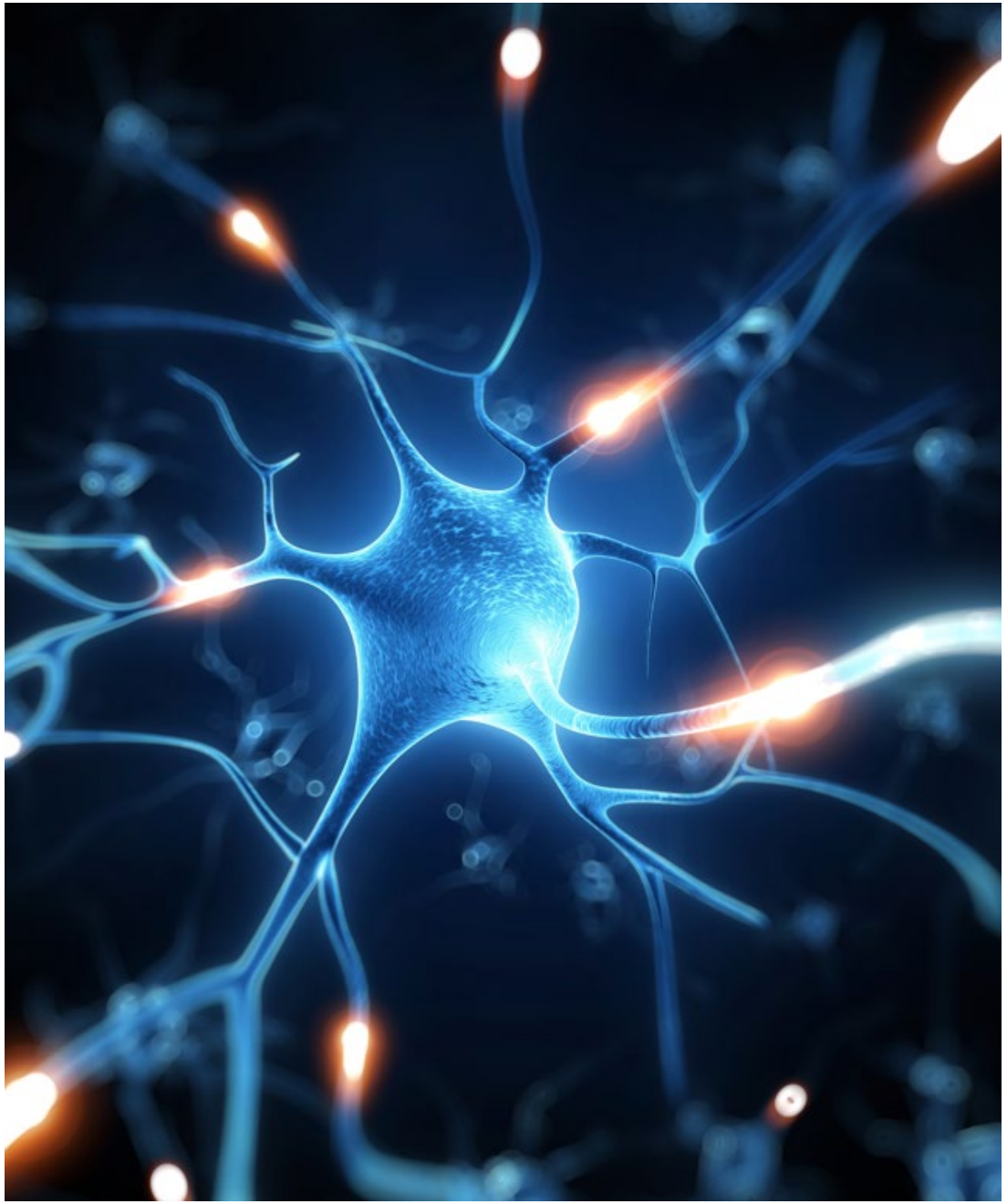
Chief of Neurology

Lexington VA Healthcare System

October 31, 2025

VA | U.S. Department of Veterans Affairs
Veterans Health Administration
Lexington VA Health Care System



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Disclosures

- None

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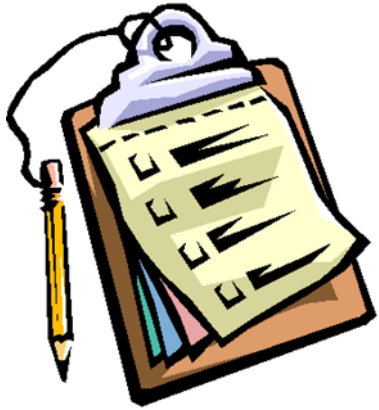
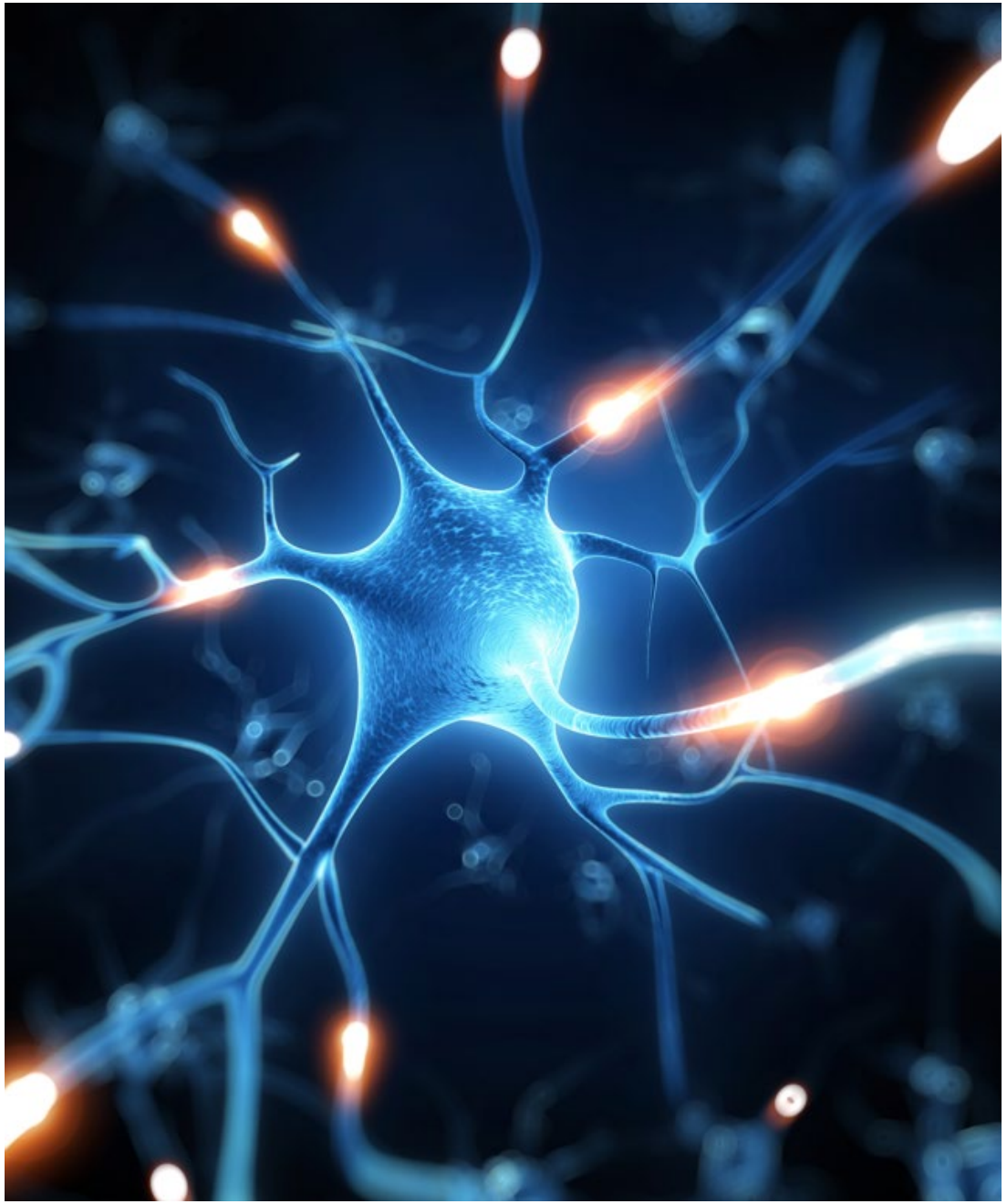
Objectives



- Overview of the current definition, updated classification of epilepsy and seizure semiology.
- Discuss the diagnostic approach to epilepsy.
- Describe management options for epilepsy- with emphasis on anti-seizure medications.

DEFINITION



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Conceptual Definition

- Seizure: Transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain

- Epilepsy: Disease characterized by an enduring predisposition to generate epileptic seizures.

Epilepsia. 2005 Apr;46(4):470-2.

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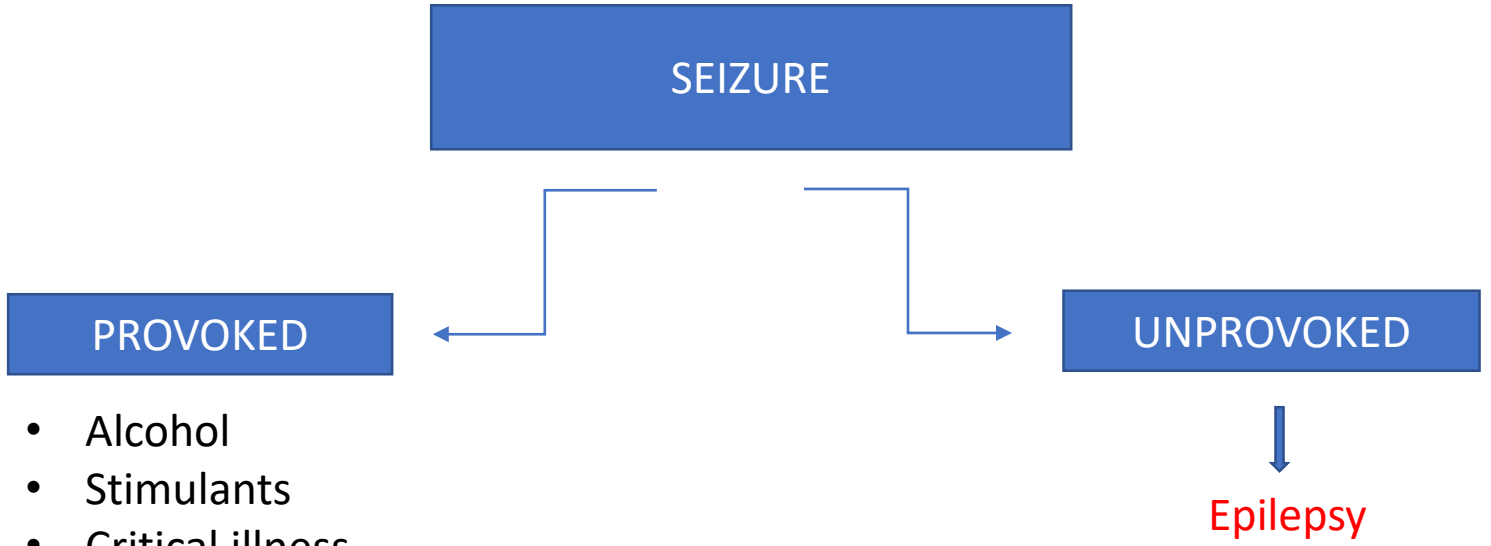
Seizure

- Seizures are very common
- 1 in 10 people can have a seizure



- Alcohol
- Stimulants
- Critical illness
- Metabolic abnormalities
- Medications

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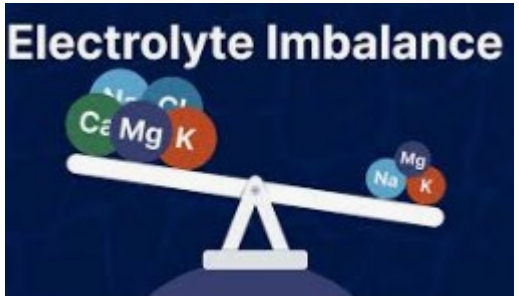
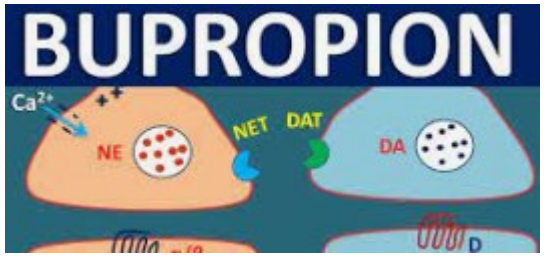
Examples of Provoked Seizures





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Practical Definition - 2014

- At least two unprovoked (or reflex) seizures occurring >24 hours apart
- One unprovoked seizure and a probability of further seizures of at least 60% over the next 10 years
- Diagnosis of an epilepsy syndrome

ILAE, Fisher et al, Epilepsia 2014, 55(4):475–482

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Epidemiology

- 3.5 million Americans (1.2% of population)
- 1 in 26 patients will be diagnosed with epilepsy in their lifetime

- Highest incidence occurs at the extremes of life

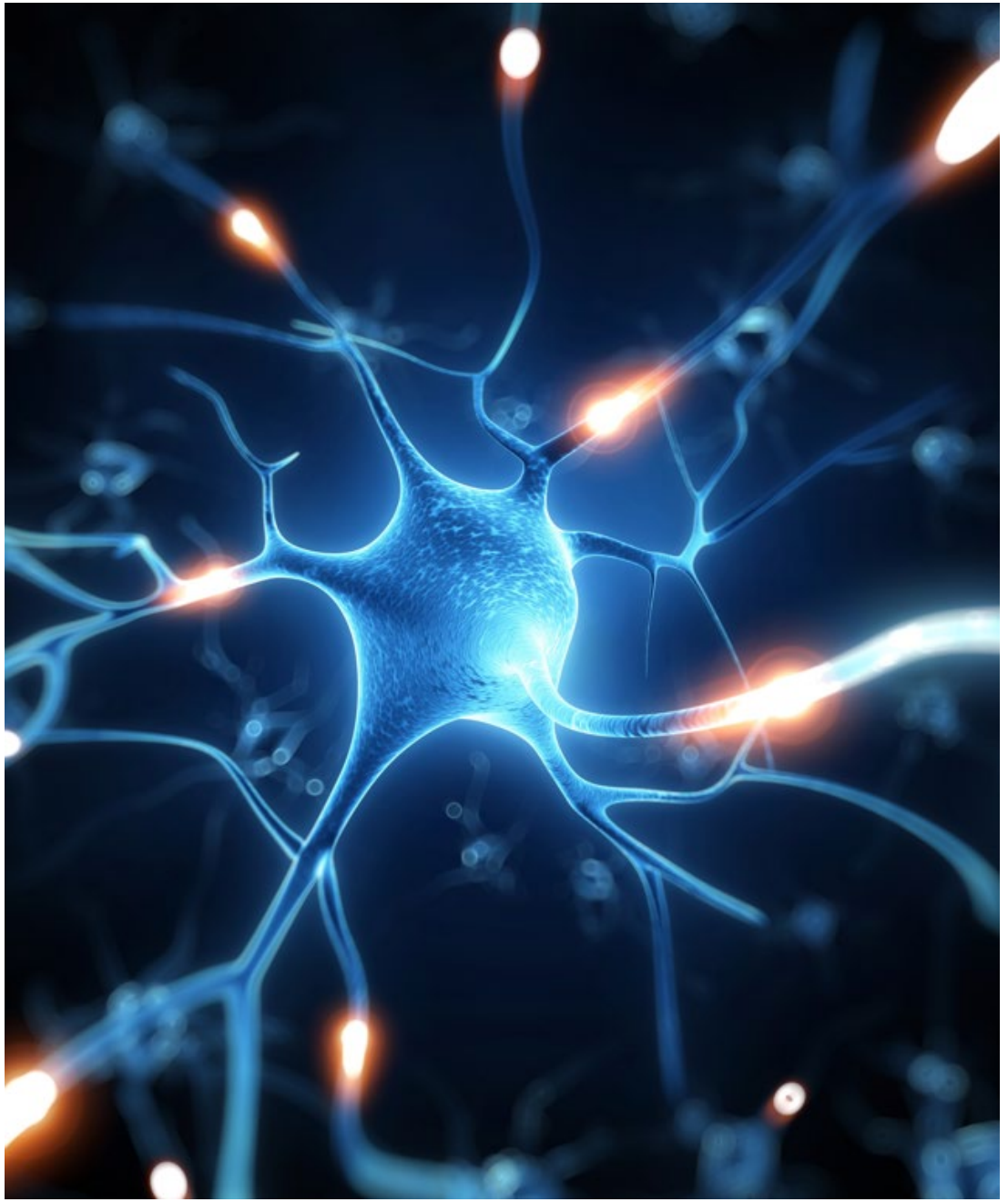
- Nearly 70% of treated epilepsy patients enter remission
- Mortality is 2-3 times higher in epilepsy patients

- Negatively effects quality of life

CDC 2017

Hauser et al; Epilepsia 2008;49(suppl 1): 8–12.

UPDATED CLASSIFICATION 2025



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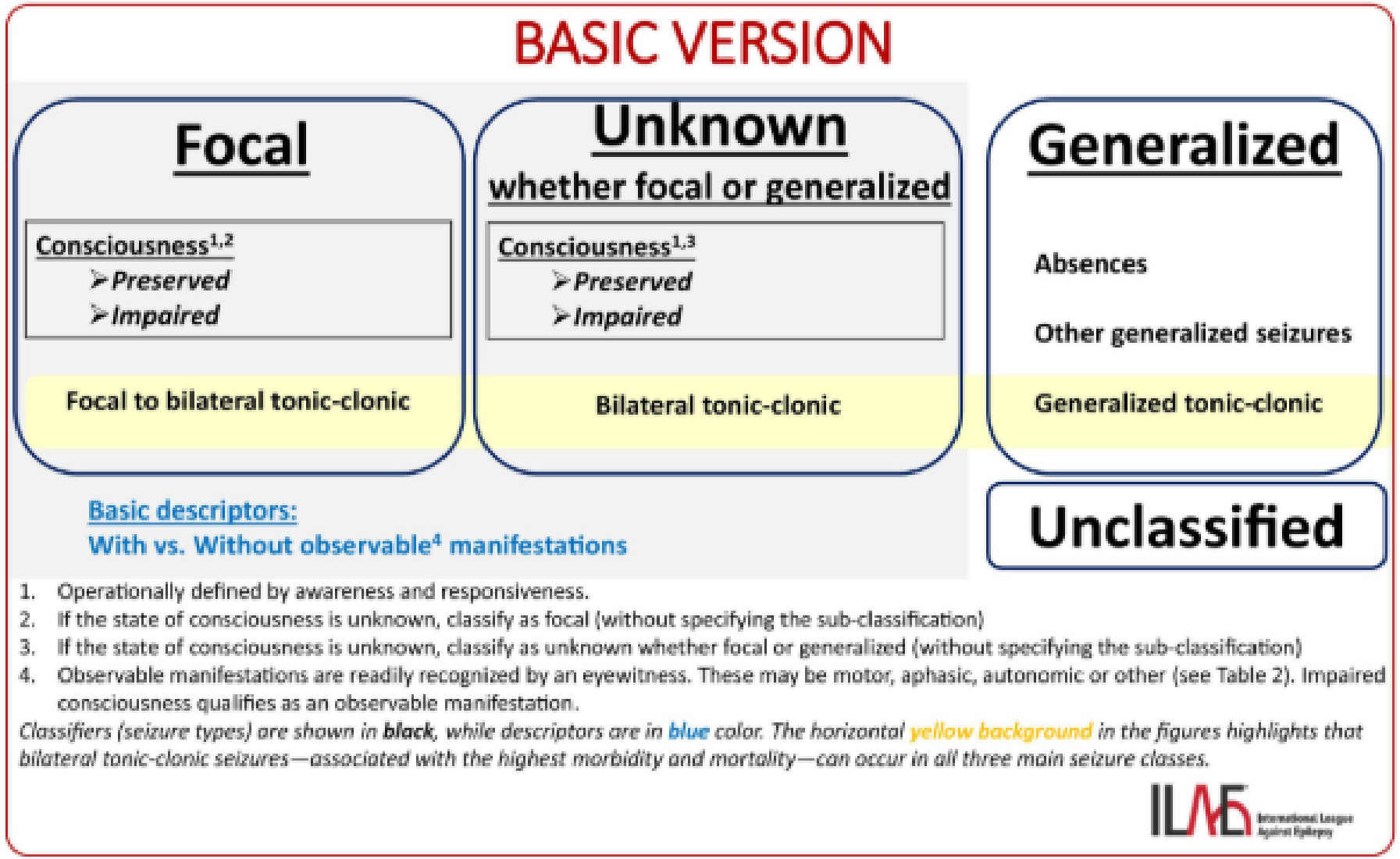
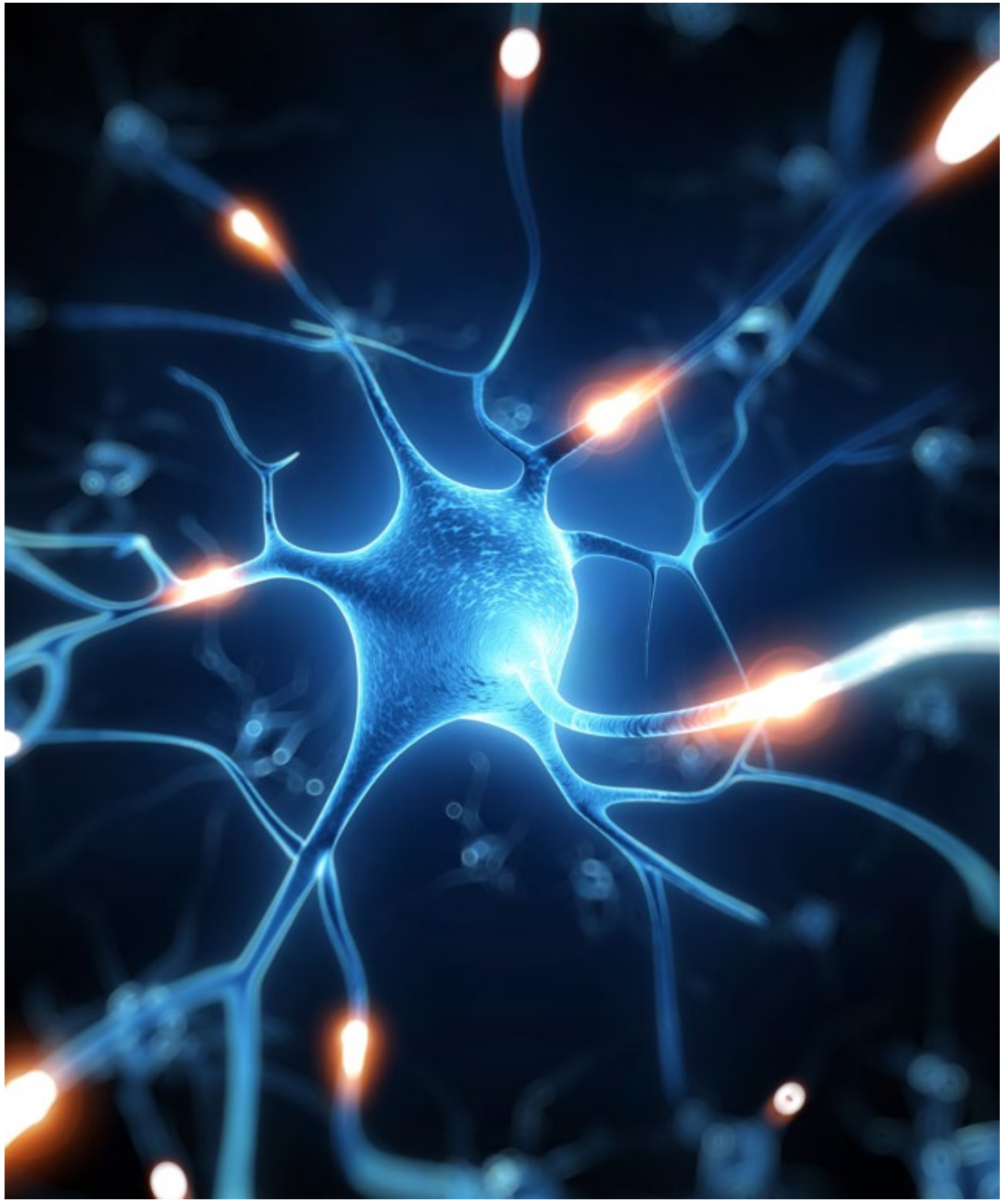


Beniczky et al; Epilepsia. 2025 Jun;66(6):1804-1823.

CLINICAL DESCRIPTION OF SEIZURES (SEIZURE SEMIOLOGY)



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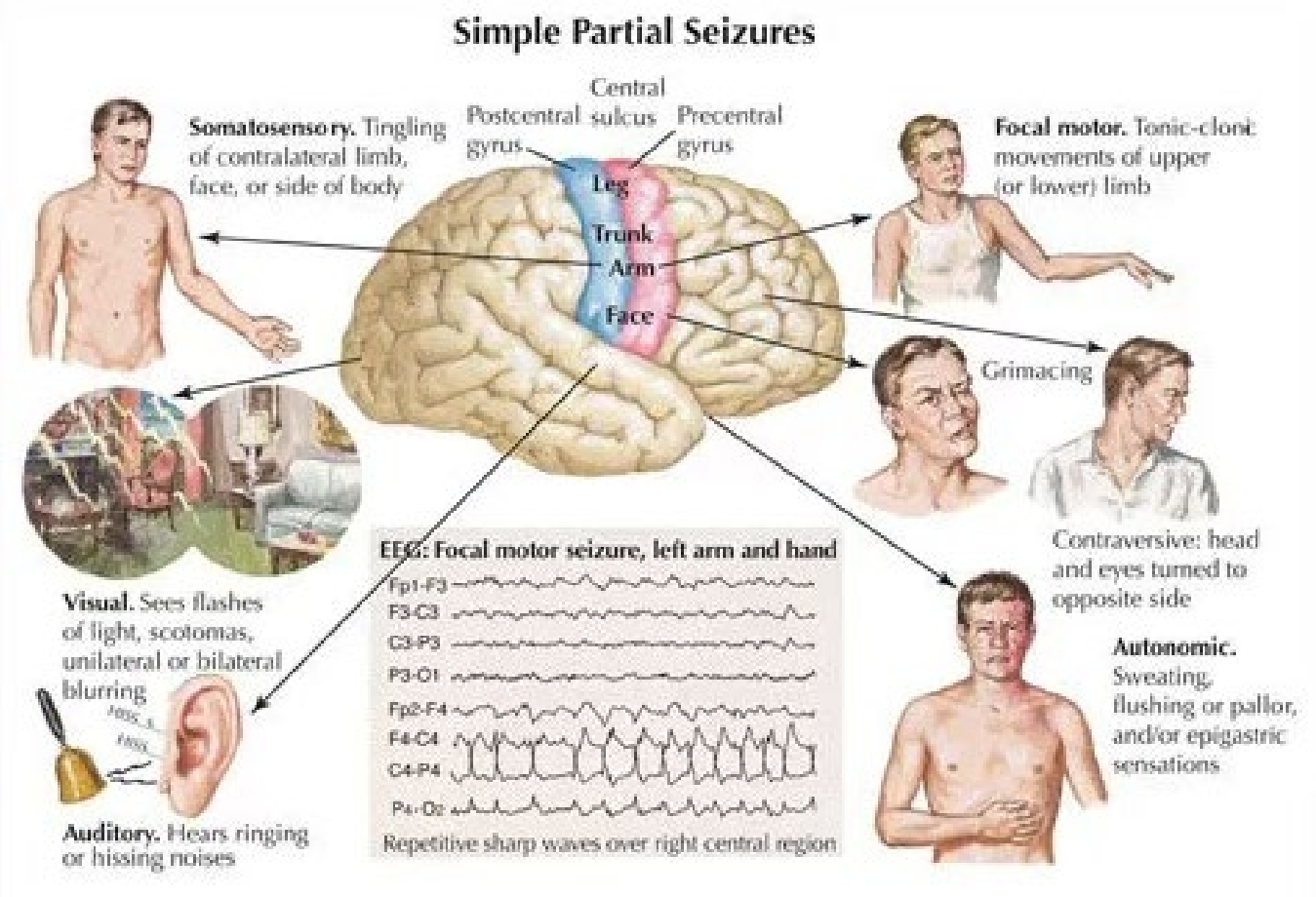
Focal Preserved Consciousness Seizure (FPC)

- Aura: Subjective sensation preceding the seizure; by itself is a focal seizure

- Temporal lobe epilepsy: 80% have auras- Déjà vu, epigastric rising sensation, distortions of time, sudden fear, metallic taste, tinnitus

- Parietal lobe: contralateral sensory symptoms

- Occipital lobe: contralateral visual symptoms



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Focal Impaired Consciousness Seizure (FIC)

- Automatisms: Repetitive involuntary semi purposeful movements
- Most common: Lip smacking, chewing, fumbling, patting, picking
- Objective signs help in lateralization and localization of seizure focus
- Eye deviation- contralateral frontal lobe
- Speech arrest- dominant temporal lobe

In this picture- seizure focus is contralateral to the extended forearm
(left frontal lobe- specifically SSMA area)

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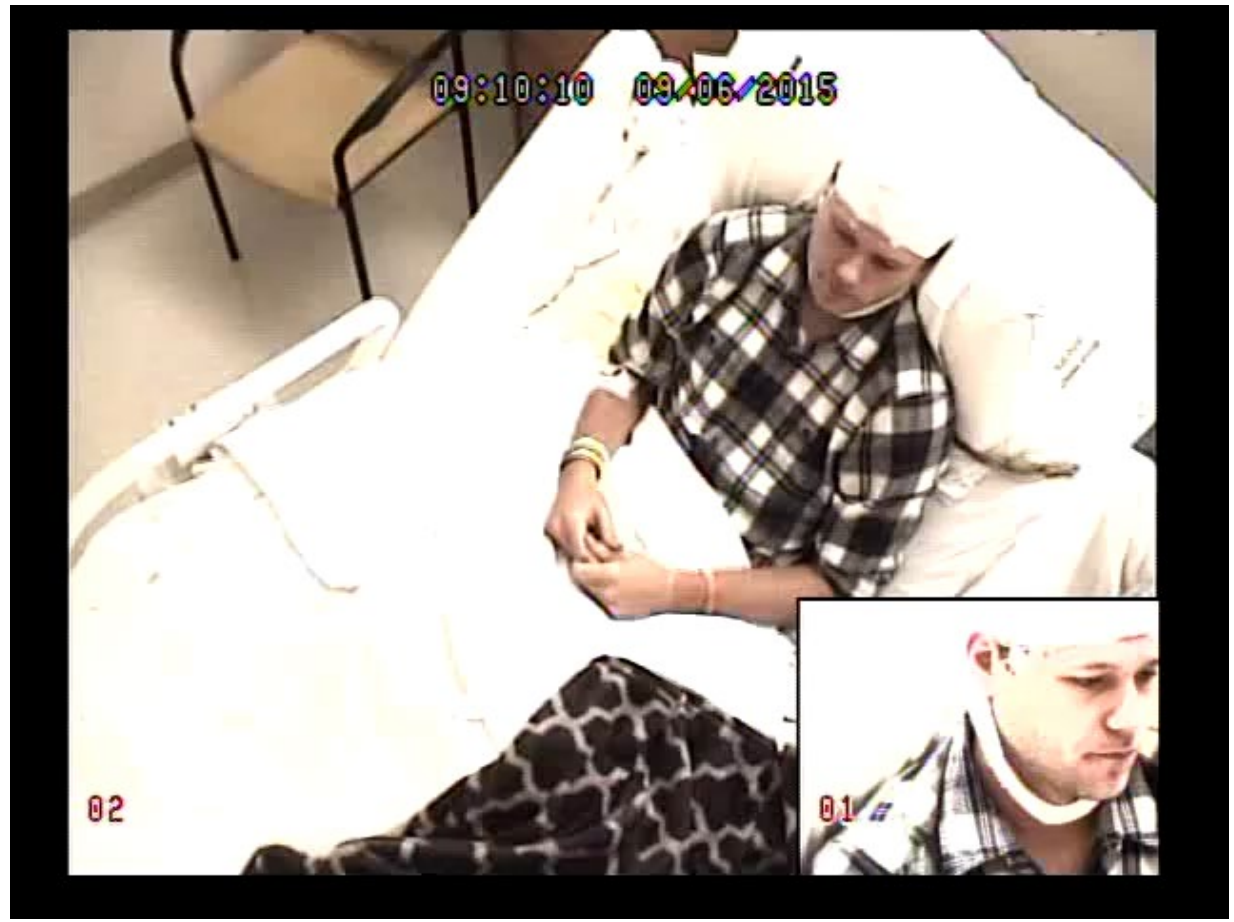

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Generalized seizures

- Generalized Tonic-Clonic (GTC) seizure (grand-mal seizure): Impairment of awareness and bilateral, often symmetric motor manifestations
- Dramatic, more chance for physical injuries
- Tonic-Clonic, Tonic, Atonic, Clonic, Myoclonic, Absence

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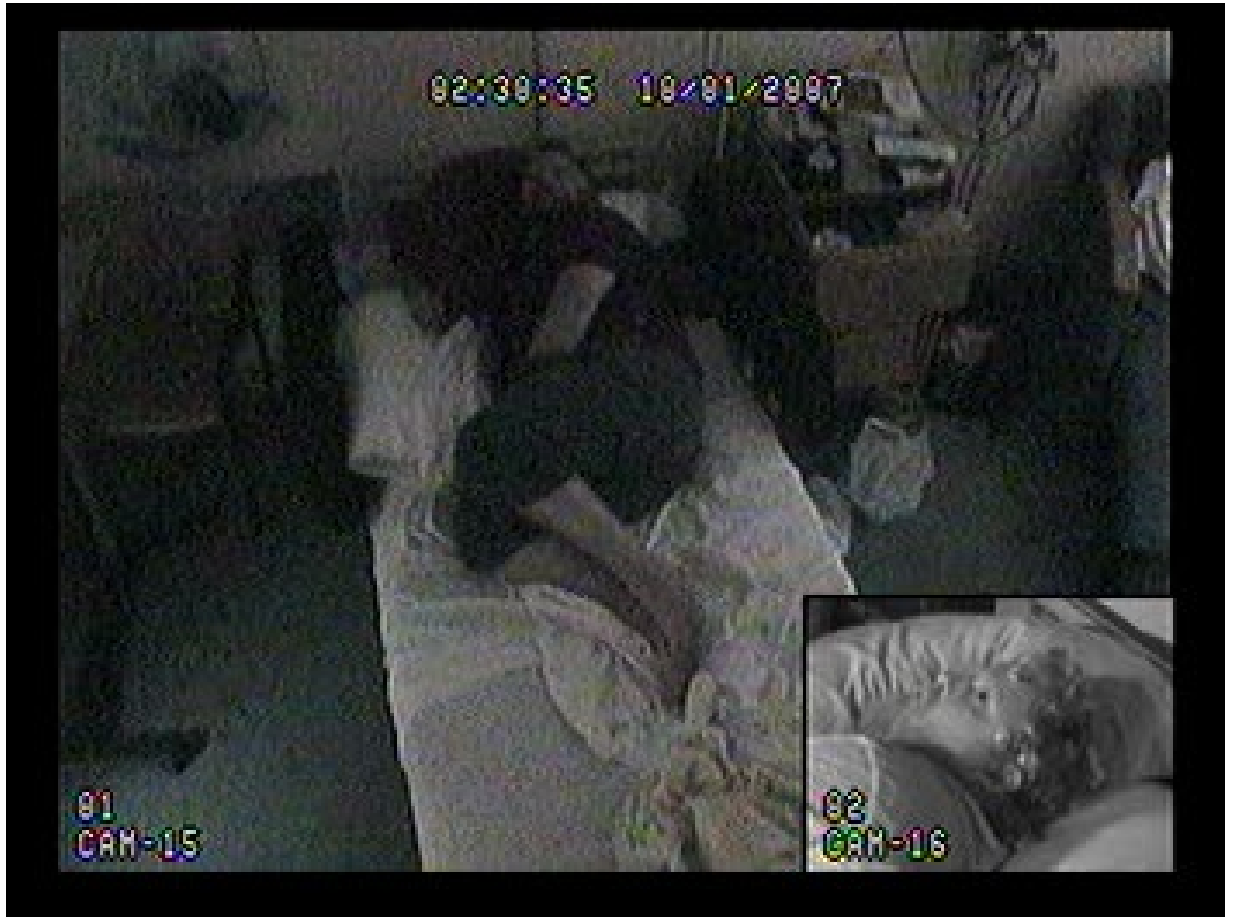

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Juvenile Myoclonic Epilepsy

- Most common genetic generalized epilepsy, 5-10%
- Onset: 12-18 years
- Females > males

- Myoclonic jerks in the morning, generalized tonic-clonic seizures
- Provoked by sleep deprivation, alcohol, exposure to flashing lights, stress

- EEG: 4-6 Hz polyspike-and-wave discharges, 50% photoparoxysmal response
- Treatment: Valproic acid, levetiracetam, lamotrigine

- Prognosis: Lifelong therapy, remission is rare

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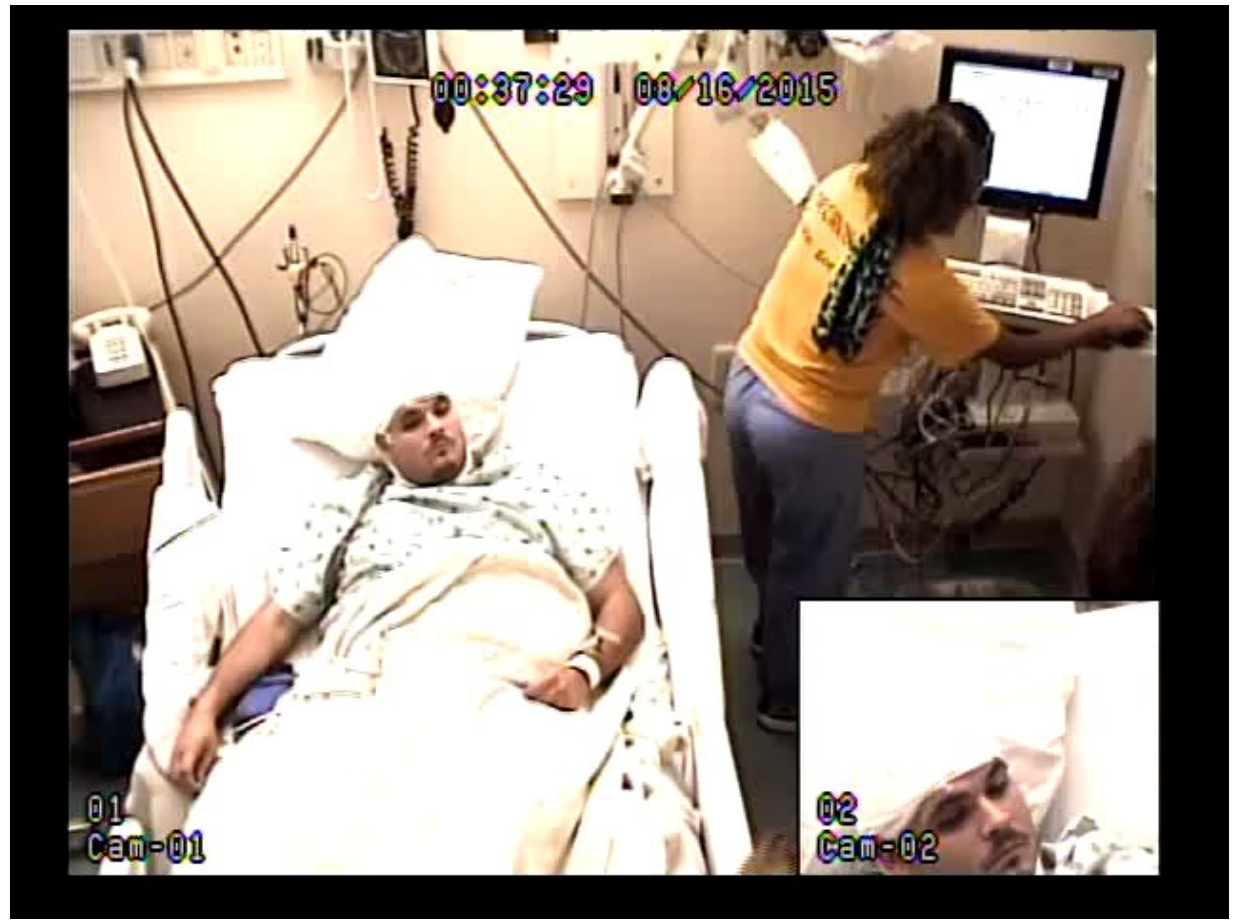
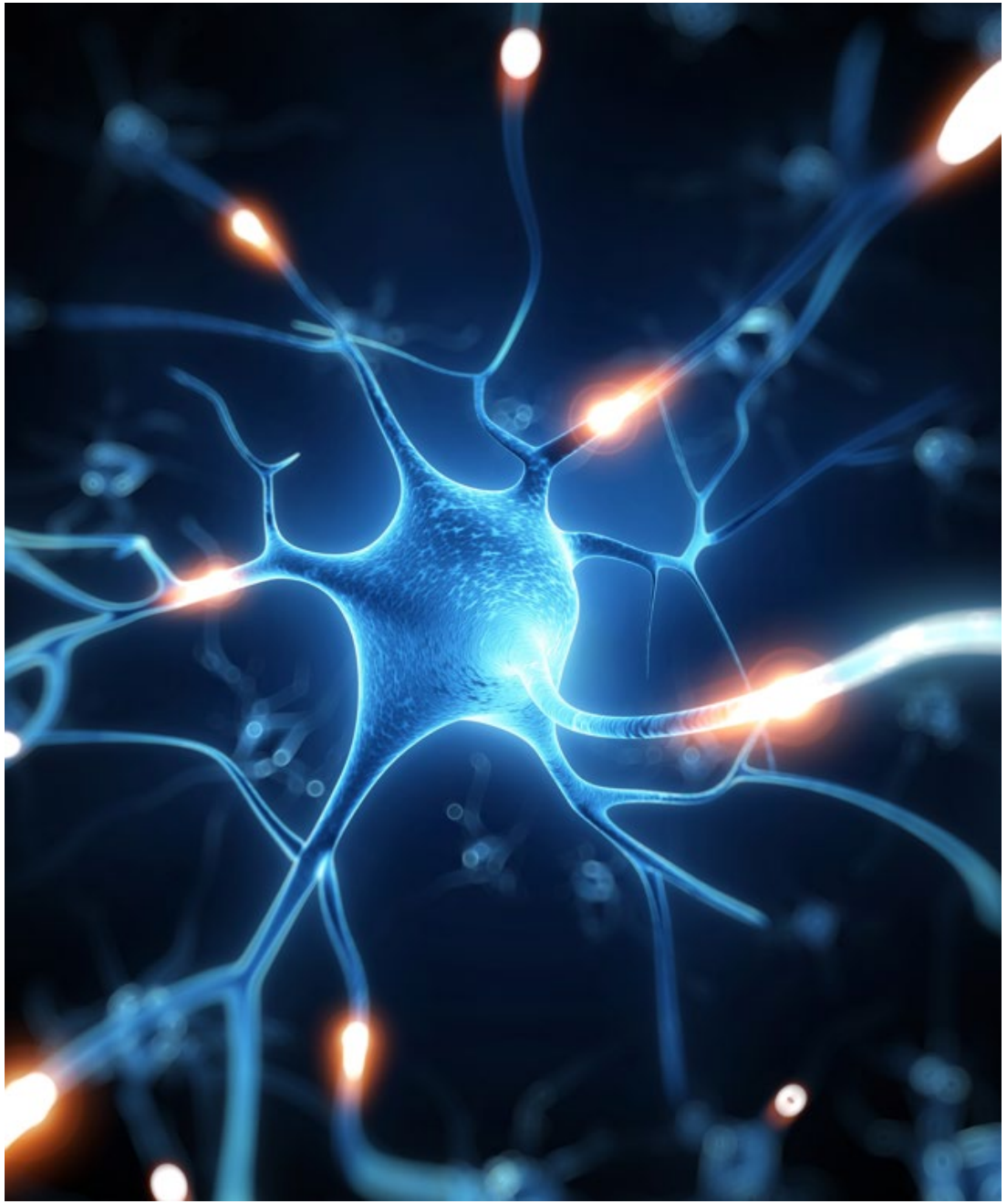


ETIOLOGY



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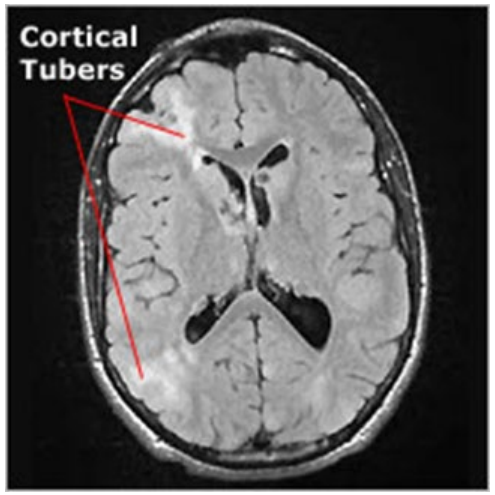


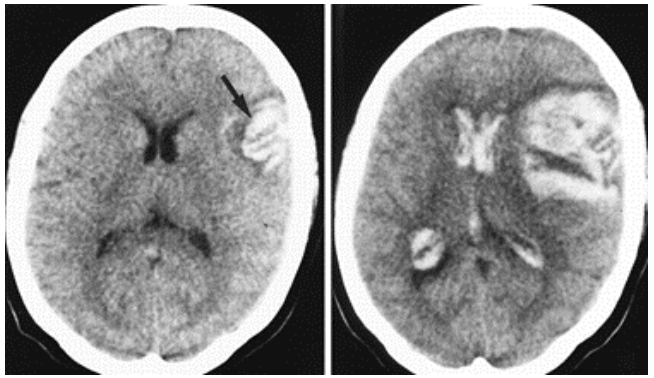
STRUCTURAL

CONGENITAL:

- Developmental Malformations- cortical dysplasia, heterotopia
- Neurocutaneous Syndromes- Tuberous Sclerosis, Neurofibromatosis

ACQUIRED:

- Stroke: Hemorrhagic > Ischemic
- Antenatal/ Perinatal insults
- Tumor, Trauma, Infections



GENETIC

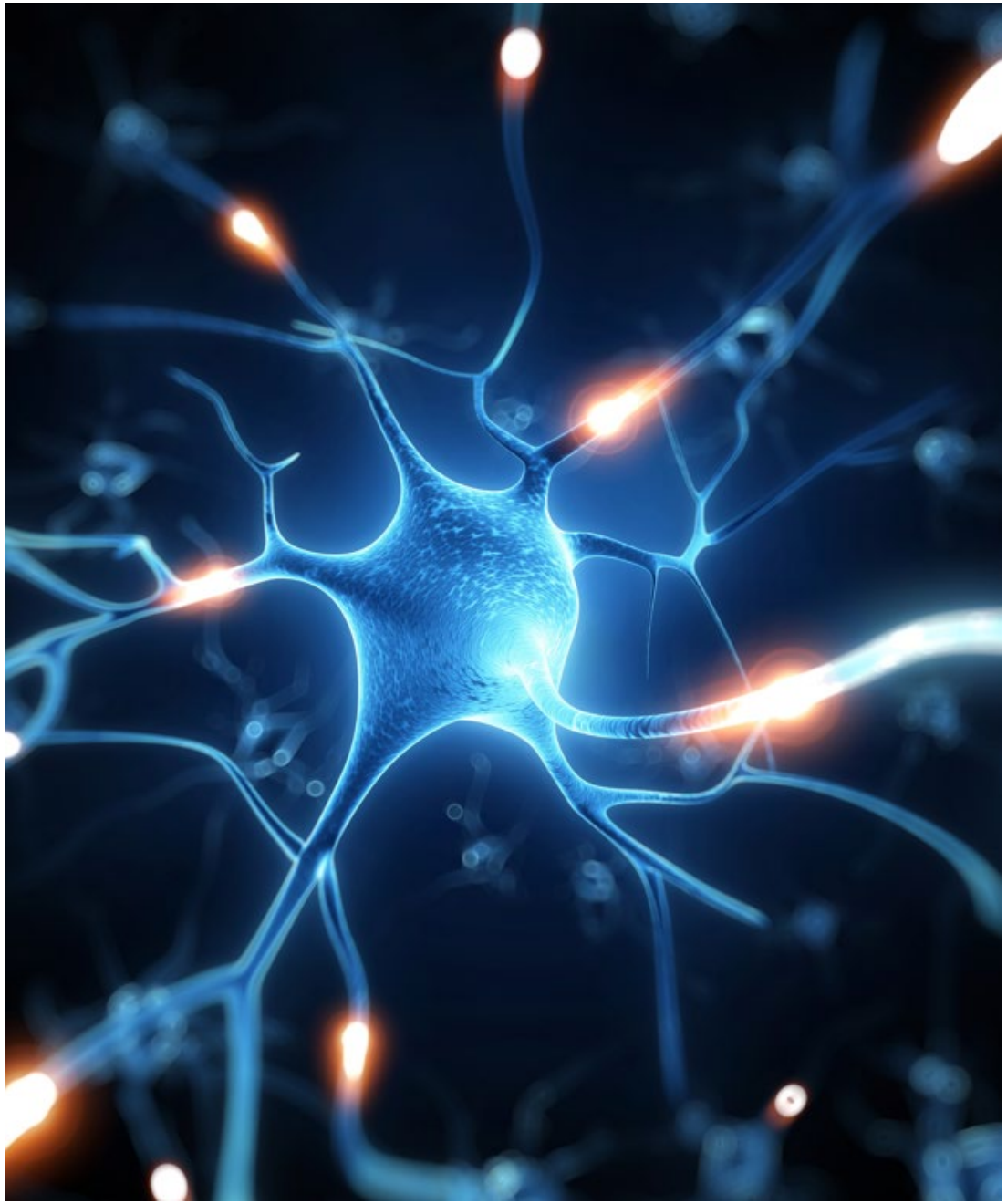
- Direct result of a known or presumed genetic defect (runs in families)
- Childhood Absence Epilepsy, or Juvenile Myoclonic Epilepsy (JME)

UNKNOWN

- About 1/3rd of the cases
- Autoimmune

SEIZURE/ EPILEPSY WORK UP

- Detailed History
- Electroencephalogram (EEG)
- MRI Brain w/wo contrast



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EEG

- Routine outpatient EEG- 20 minutes to 2 hours to start with

- **What do EEG results mean and what should you do about them?**
- Seizures and epileptiform abnormalities (sharps/ spikes/ spike-and-wave)- TREAT, don't wait
- Focal slow activity (cerebral dysfunction)- indicates possible structural abnormality, get an MRI brain, do not treat
- Generalized slow activity- no not treat

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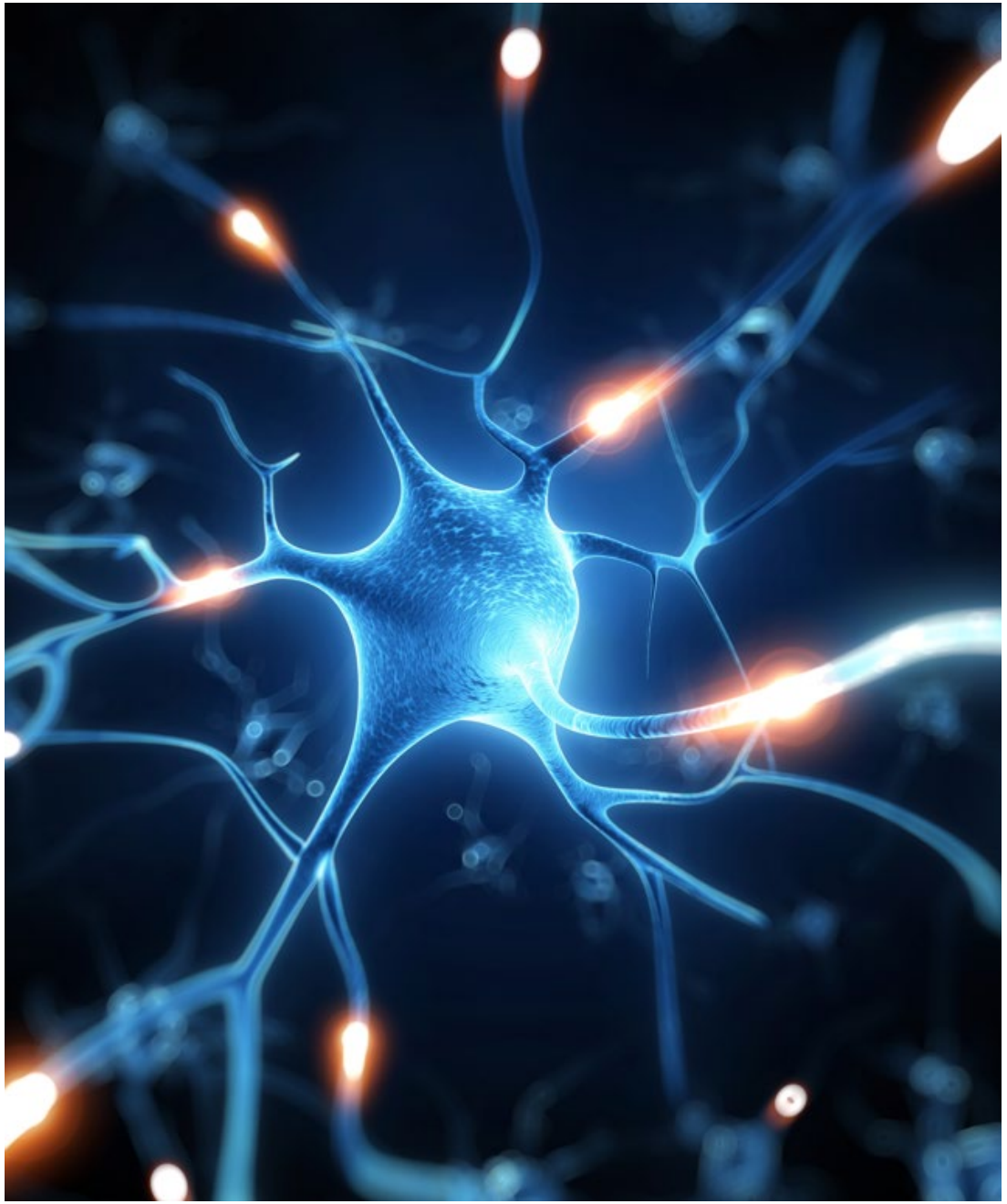
Neuroimaging

- MRI brain- best for localizing the lesion
- With contrast only if tumor is suspected, prefer W/O contrast

- CT head- Not ideal for routine use
- ER setting, suspected bleed

APPROACH TO FIRST SEIZURE



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Classification of a First Seizure

- Provoked seizure (toxin, medication, or metabolic factors)

- Brain Insult:
- Acute- stroke, trauma, intracranial infection
- Remote- preexisting brain injury (very high risk of seizure recurrence!)

- Genetic- Epileptic syndrome (JME)

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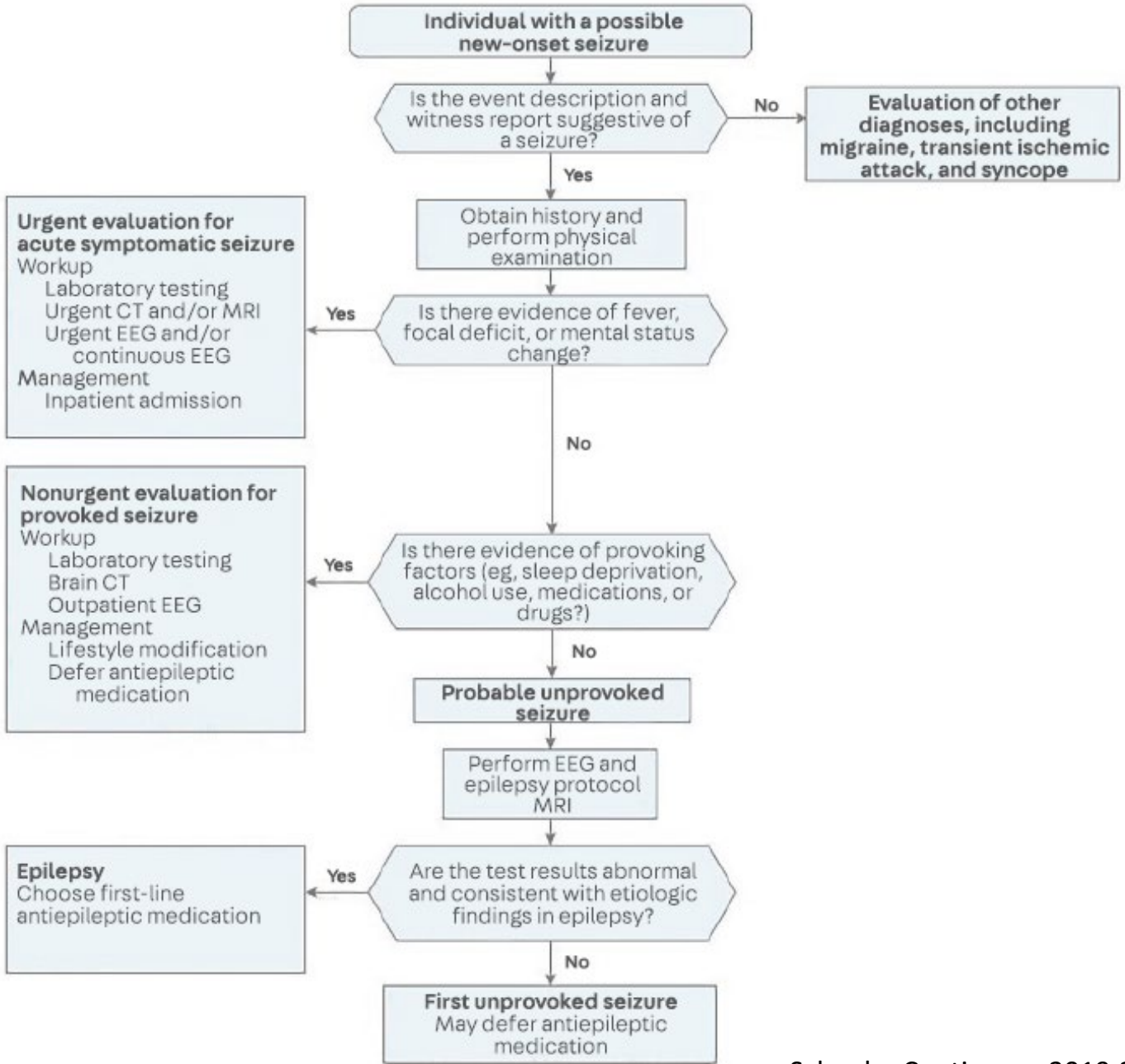

Schuele; Continuum 2019;25(2, EPILEPSY):322–342.

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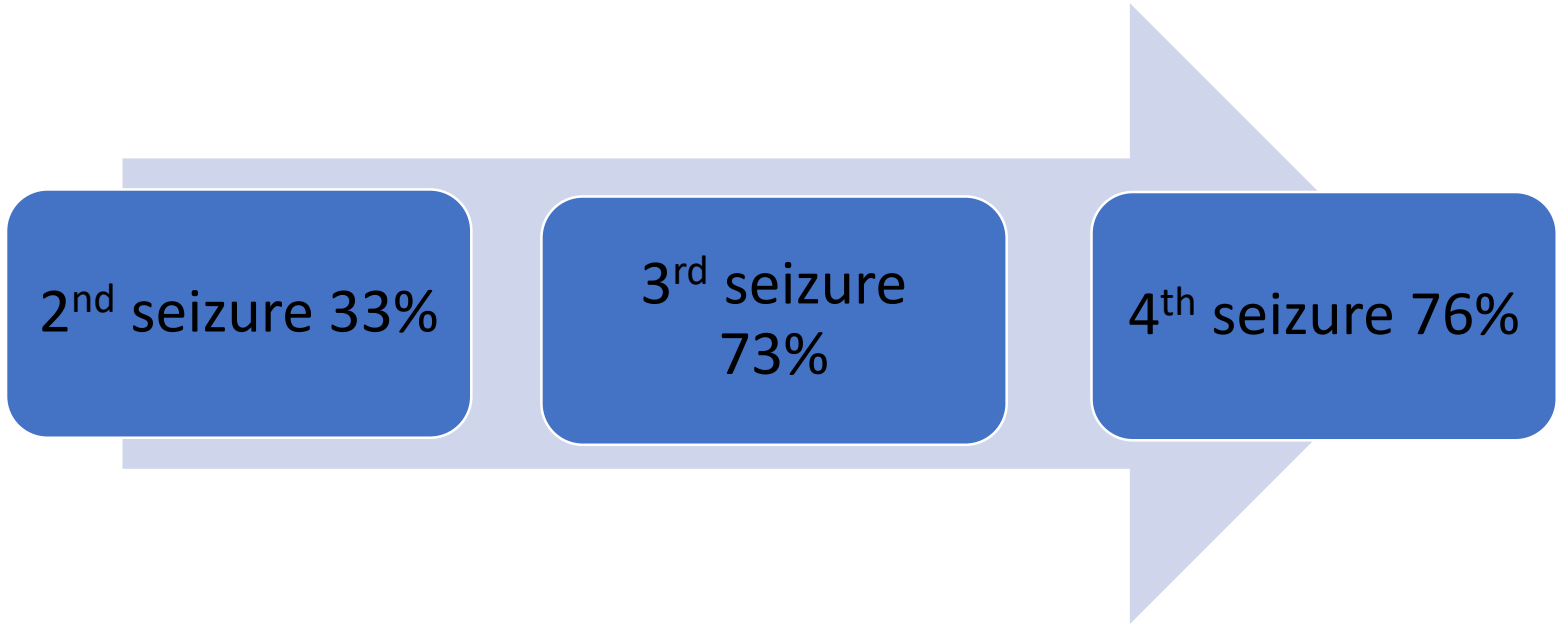
Recurrence risk after first unprovoked seizure

- Hauser et al, 1998 - prospective study
- n= 204



Hauser et al. Risk of recurrent seizures after two unprovoked seizures. NEJM 1998;338:429.

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Evidence-Based Guideline: Management of an Unprovoked First Seizure in Adults

Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society

A. Krumholz, MD[1,2]; S. Wiebe, MD[3]; G. S. Gronseth, MD[4]; D. S. Gloss, MD[5]; A. M. Sanchez, MD[1]; A. A. Kabir, MD[1]; A. T. Liferidge, MD[6]; J. P. Martello, MD[1]; A. M. Kanner, MD[7]; S. Shinnar, MD, PhD[8]; J. L. Hopp, MD[1]; J. A. French, MD[9]
[1]Department of Neurology, Maryland Epilepsy Center, University of Maryland School of Medicine, Baltimore
[2]US Department of Veterans Affairs, Maryland Healthcare System, Epilepsy Center of Excellence, Baltimore
[3]Department of Clinical Neuroscience, University of Calgary Faculty of Medicine, Canada
[4]Department of Neurology, University of Kansas School of Medicine, Kansas City, KS
[5]Department of Neurology, Geisinger Health System, Danville, PA
[6]Department of Emergency Medicine, George Washington University School of Medicine, Washington, DC
[7]Department of Neurology, International Center for Epilepsy, University of Miami Miller School of Medicine, FL
[8]Departments of Neurology, Pediatrics, and Epidemiology & Population Health, Albert Einstein College of Medicine, Yeshiva University, Bronx
[9]New York University Comprehensive Epilepsy Center, New York, NY

Level A – Strong Evidence
Level B – Moderate Evidence
Level C – Weak Evidence

Conclusion:

- Adults with an unprovoked first seizure should be informed that seizure recurrence risk is greatest early within the first 2 years (21%–45%) (Level A), and **clinical variables associated with increased risk may include:**
  - a prior brain insult (Level A),
  - an epileptiform EEG (Level A),
  - an abnormal CT/MRI(Level B)
  - a nocturnal seizure (Level B)

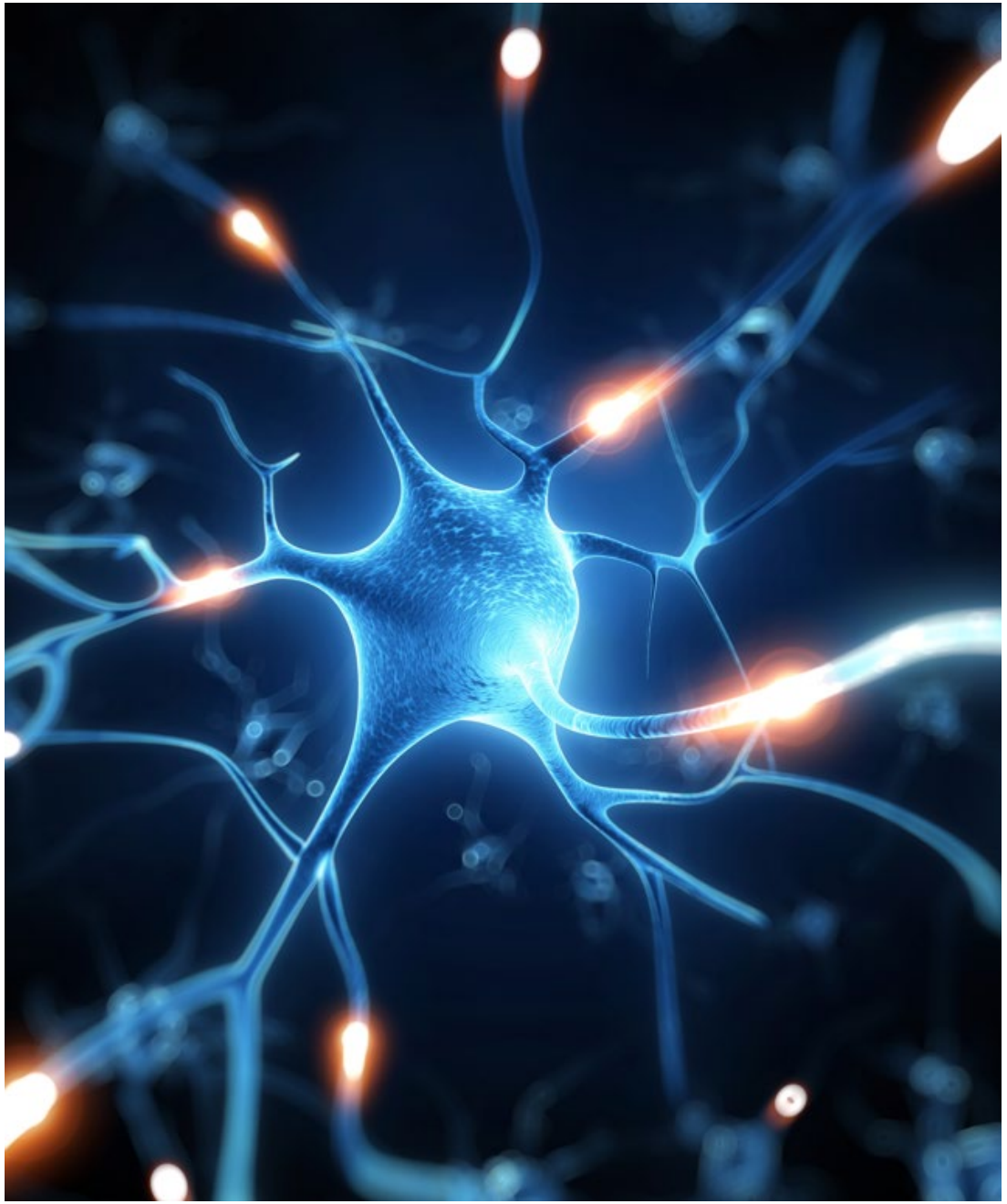
TREATMENT OPTIONS

1. MEDICATIONS- ASM/AED

2. NEUROMODULATION- VNS, RNS, DBS

3. SURGERY

4. DIET



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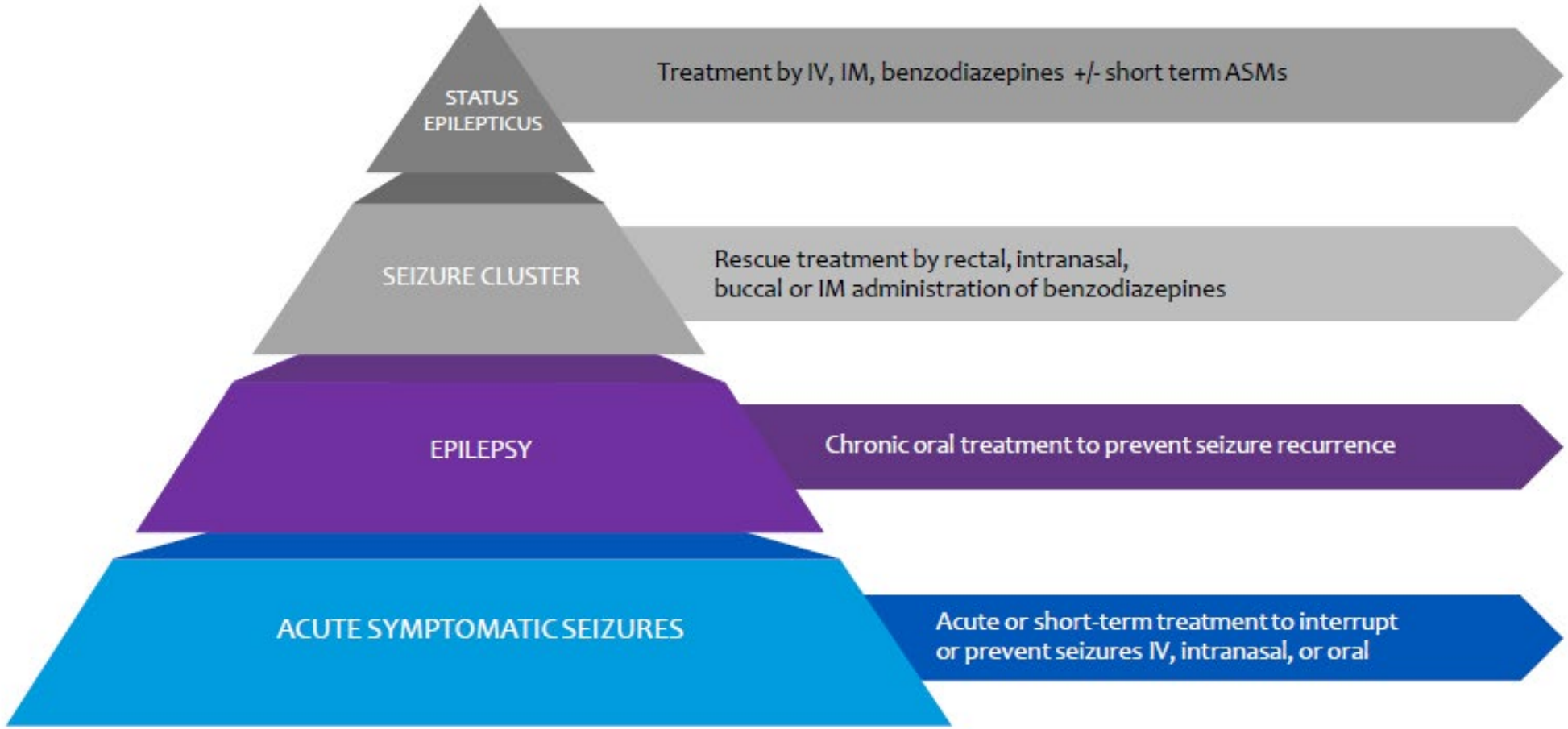
Spectrum of ASMs



Löscher, W., Klein, P. *CNS Drugs* 35, 935–963 (2021)

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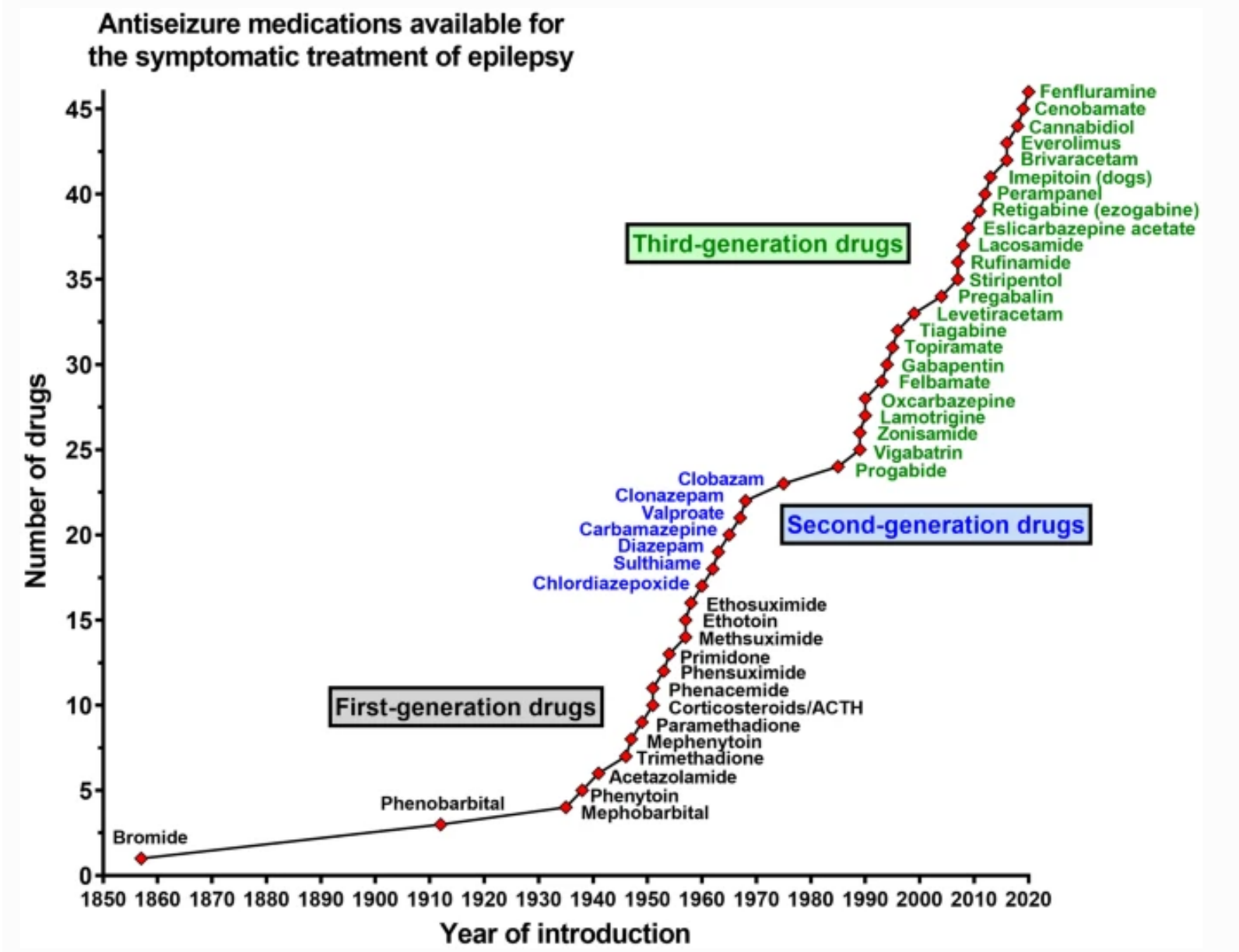

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Goal of ASM – Ideal ASM

- Freedom from disabling seizures
- Minimal therapy related side effects
- Prevention and treatment of comorbidities
- Prevention of mortality (SUDEP) and maximize quality of life

Moshe et al., 2015. Lancet 385:884-898.
Kalilani et al., 2018. Epilepsia 59:2179-2193.
Verducci et al., 2019. Neurology 93:e277-e236

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General Tips for ASM's

- Broad Spectrum ASM may be the best to start

- Do not start a very high dose right away
- Only exception is status epilepticus, seizure clusters or GTC seizures

- Be familiar with and explain to patients about common side effects

- Always warn patients about mood related side effects

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ASM's for New Onset Epilepsy

	NARROW SPECTRUM FOCAL SEIZURES	BROAD SPECTRUM GENERALIZED/ UNKNOWN SEIZURES
1ST	Levetiracetam (LEV), Lamotrigine (LTG), Oxcarbazepine (OXC) Lacosamide (LCM)	LEV, LTG, Topiramate (TPM), Zonisamide (ZNS), Valproic Acid (VPA)
2ND	ZNS, TPM, VPA Eslicarbazepine (ESLI), Brivaracetam (BRIV)	LCM, Perampanel (PER)
3RD	Cenobamate (XCOPRI), Clobazam (CLB), Pregabalin (PGB), Perampanel (PER)	CLB
Bottom	Phenytoin (PHT), Carbamazepine (CBZ) Lorazepam (LZP), Clonazepam (CLP)	LZP, CLZ
Almost Never	Felbamate (FBM), Phenobarbital (PB), Gabapentin (GBP)	

ASM
Q & A

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Question # 1

- I help both generalized and focal seizures, commonly prescribed because I am considered a very safe medication. Asthenia and mood issues are my most common side effects. Quick titration and IV and PO formulations make me very popular in clinic, ER and inpatient settings. Who am I?

1. Lamotrigine (Lamictal)
2. Levetiracetam (Keppra)
3. Oxcarbazepine (Trileptal)
4. Phenytoin (Dilantin)
5. Valproic Acid (VPA)

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Levetiracetam (Keppra)
FIRST LINE FOR EVERYTHING

- Unique mechanism of action- blocks the SV2 a receptors
- Broad spectrum, focal and generalized, magic for myoclonic seizures!

- PO and IV
- Safe as first choice for new onset seizures (500 mg BID), seizure clusters (1000 mg IV) and status epilepticus (40 mg/kg IV load)

- Renally cleared; No interactions, can start at target dose!!!

- Most common side effect: Asthenia
- Do not use: Mood issues, SI or HI

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Question # 2

- I have been famous since the 1970's, broad spectrum, and the drug of choice for JME. I will haunt your exams with the neural tubal defect question, so please do not prescribe me to women of reproductive age. Try me at high doses and see the liver enzymes skyrocket. Oh, did you know I also cause thrombocytopenia? So please check both CBC and CMP on your chronic patients. Who am I?

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Valproic Acid (VPA)

- Multiple mechanisms of action, broad spectrum
- Both PO and IV form
- Used to be first line for generalized epilepsies

- Most common side effect:
- Tremor!
- Other side effects: Weight gain, alopecia
- Monitor: Platelets, Liver Enzymes (dose dependent)
- Ammonia only if patient c/o somnolence/ encephalopathy

- Highly teratogenic, causes NTD's in fetus, ID/ autism in children exposed to VPA in utero; make sure young women are on folic acid if on VPA
- Best avoided in primary care, defer to neurology to start VPA

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Question # 3

- I am a favorite of epileptologists, but others ignore me because I am too slow to titrate. I wish people were patient with me, because I am known to be a safe and effective, broad spectrum ASM. With mood stabilizing and cognitively stimulating properties, I should be your first choice in the clinic setting. But if you're in a hurry to increase my dose, I will most definitely cause a skin rash and Steven Johnson's Syndrome. Who am I?

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Lamotrigine

- Winner in safety, efficacy and tolerability in most studies of ASM's
- Broad spectrum
- Mechanism: sodium channel blocker

- Excellent mood stabilizer
- No need for chronic labs or levels in most cases
- Only exception: Estrogen/ combined HCP's- ↓ level of lamotrigine

- Rapid titration: Skin rash and/or SJS
- Start at 25 mg and increase by 25 mg weekly to reach 100 mg BID (6-8 weeks)
- Limited use in hospital setting, but ideal for clinic

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Question # 4

- Famous since the 1970's for the treatment of focal seizures, I have been reformulated twice. I have a laundry list of chronic side effects- most common being brain fog. Please monitor sodium level once every 6 months. And watch out before prescribing those pesky meds that work on the CYP enzymes… You're so lucky to not have to commonly prescribe me anymore, who am I?

  Hint: I am your go-to for the treatment of trigeminal neuralgia.

1. Lamotrigine (Lamictal)
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3. Carbamazepine (Tegretol)
4. Phenytoin (Dilantin)
5. Valproic Acid (VPA)

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Question # 4

- Famous since the 1970's for the treatment of focal seizures, I have been revised and reformulated twice since. I have a laundry list of chronic side effects- most common being brain fog. Please monitor sodium level once every 6 months. And watch out before prescribing those pesky meds that work on the CYP enzymes… You're so lucky to not have to commonly prescribe me anymore, who am I?

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Carbamazepine (CBZ)

- Narrow spectrum, only for focal seizures
- Can make generalized seizures worse!
- Sodium channel blocker, notorious for interactions

- Hyponatremia, agranulocytosis, osteoporosis
- Check CBC/ BMP every 6 months, DEXA once in 2 years
- Calcium/ vitamin D supplementation routinely
- Advise no smoking while on CBZ

- If you must prescribe: Use the ER formulation, 100 mg BID
- Autoinduction
- Do not stop abruptly!

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Related to CBZ- only use for focal epilepsy

- Oxcarbazepine (Trileptal):
- Higher chance of hyponatremia
- But lower osteoporosis and somnolence
- Mood stabilizing properties
- Best avoided in anyone >50 years of age

- Eslicarbazepine (Aptiom):
- Once daily
- Lowest side effects
- Monitor sodium!

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Question # 5

- I am very popular among residents while they're on-call, but most of them are not aware that I can cause phlebitis/ cellulitis and purple glove syndrome when given IV. Many a times, with infusions, I result in hemodynamic instability. My long-term side effects are many, yet, I remain popular.

  Guess my name!

a) VPA
b) Phenytoin
c) Levetiracetam
d) Lacosamide
e) Phenobarbital

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Question # 5

- I am very popular among residents while they're on-call, but most of them are not aware that I can cause phlebitis/ cellulitis and purple glove syndrome when given IV. Many a times, with infusions, I result in hemodynamic instability. My long-term side effects are many, yet, I remain popular.

  Guess my name!

a) VPA
b) Phenytoin
c) Levetiracetam
d) Lacosamide
e) Phenobarbital

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Phenytoin

- **Dose-related toxicity:** N/V, CNS depression, nystagmus (20µg/ml), ataxia (30µg/ml)
- **Chronic toxicity:** gingival hyperplasia, hirsutism, peripheral neuropathy (motor>sensory), vitamin D deficiency and osteomalacia/osteoporosis
- Irreversible cerebellar degeneration/ ataxia
- **IV formulation has propylene glycol → cardiac toxicity and tissue necrosis**
- **Phenytoin encephalopathy:** Mental status changes, ataxia, slow activity on EEG, increased seizure frequency

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Phenytoin

- Labs: CBC/ CMP every year, DEXA every 2 years

- Levels: if concern for toxicity
- Non-linear kinetics: small dose increase → steep increase in level

- CYP enzyme inducer → interactions!

- Prescription of phenytoin is best avoided

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Question # 6

- I am well known for being broad spectrum, but I can really slow you down, make you blind and writhe in pain due to kidney stones. Although, people love me as I make them lose weight.

  What's my name?

a) Topiramate
b) Lacosamide
c) Levetiracetam
d) Primidone
e) Clobazam

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Topiramate and Zonisamide

- Similar family, multiple mechanisms of action
- Broad spectrum
- Mostly prescribed PO

- Cognitive slowing, acute angle glaucoma
- Renal calculi → dose dependent, avoid carbonated drinks
- Weight loss

- Zonisamide is attractive- once daily dosing, 100-200 mg once daily
- Causes anhidrosis

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Question # 7

- I have quickly become a favorite of neurologists. Available in PO and IV formulations, I am very effective for focal epilepsy and focal status epilepticus. Careful before giving a big IV load, I can cause PR interval prolongation. With least number of chronic side effects, I do cause dizziness, which is dose dependent. Start low and go slow will be the mantra with me. Who am I?

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d) VPA
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Lacosamide

- Sodium channel blocker, narrow spectrum
- Very effective for focal epilepsy
- PO and IV

- Well tolerated, easy to titrate, no chronic side effects
- Most common side effect: Dizziness
- No need to monitor labs or level

- Prolongs PR interval with IV load- get EKG before a large dose

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Newer ASM's and important info

- Brivaracetam- similar to levetiracetam, 20 times more potent, fewer mood side effects
- Perampanel (Fycompa)- Aggression, Homicidal ideation
- Epidiolex (CBD oil)- increased appetite, LFT's
- Clobazam (Onfi)- Very effective ASM, benzo
- Cenobamate (Xcopri)- Once daily, well tolerated!

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Rescue ASM's for seizure clusters/ status epilepticus

- Rectal diazepam (old) → Intranasal midazolam or diazepam
- Pre-measured dose, 5-20 mg

- Clonazepam ODT

- Rapid onset, prevents ER visits
- Patients love the rescue option

Gidal et al, Epilepsia 2022;63(Suppl. 1):S34–S44

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Suggested Approach to Management of New Onset Seizures

- If just one seizure, order routine EEG, MRI brain w/wo contrast and refer to neurology
- If more than 1 seizure (includes simple partial seizures), order work up as above, and start an ASM

- Broad Spectrum ASM is the best to start

- LEV 500 mg BID is the safest as long patient does not have SI, or extreme anxiety
- Zonisamide 100 – 200 mg QHS is another safe alternative
- Lamotrigine- be careful of titration, a very safe ASM

- In the elderly → start low and go slow, avoid CBZ/ OXC/ Phenytoin

Deng et al; Prim Care. 2024 Jun;51(2):211-232.

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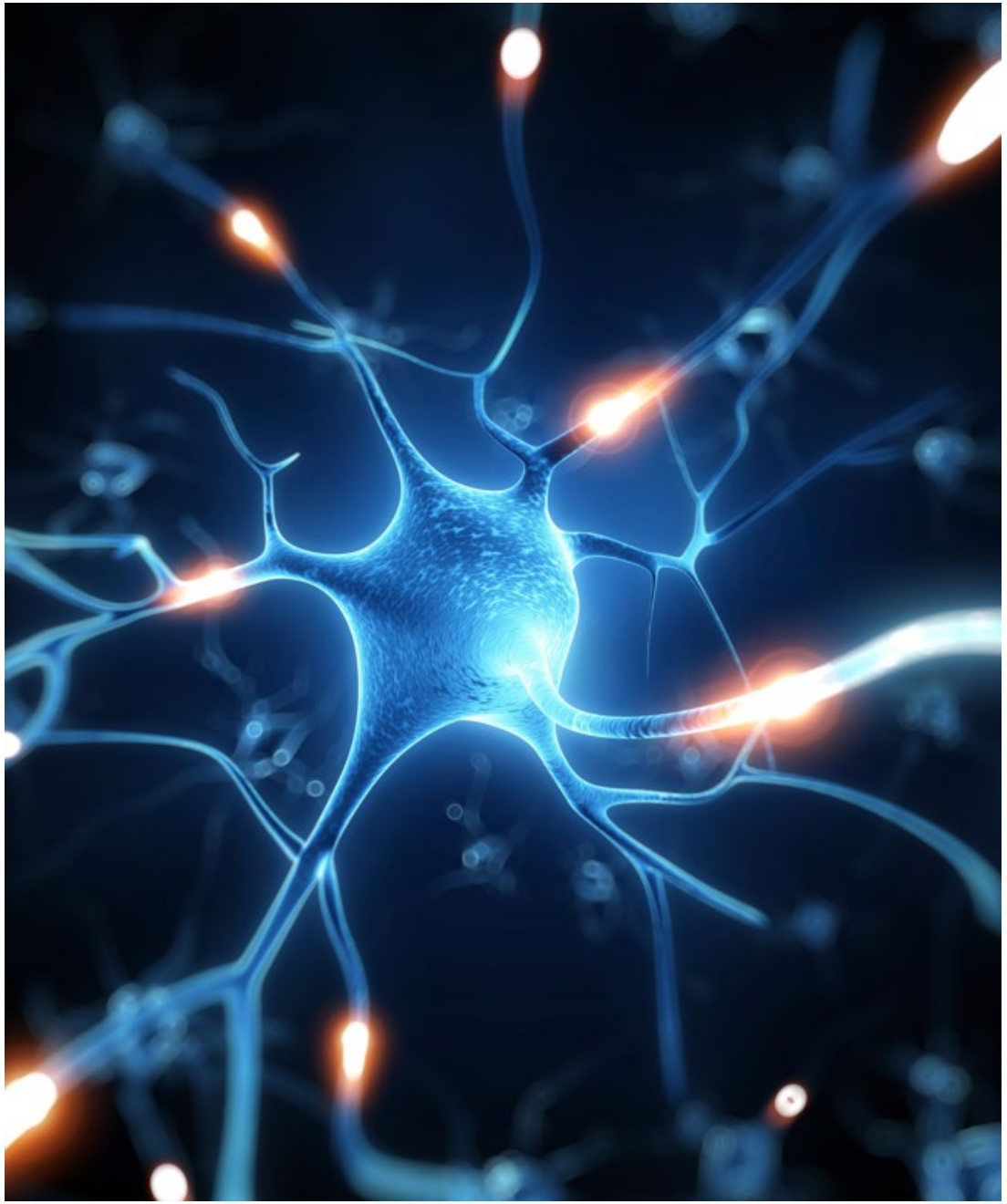
When to check levels of ASM's?

- Symptoms of toxicity- somnolence, dizziness/ imbalance, nystagmus or new tremor on exam
- Non-adherence/ breakthrough seizures
- Woman of reproductive age group and planning to get pregnant- obtain a baseline level
- Pregnancy
- Elderly patients (age >75)

WHEN MEDICATIONS DON’T WORK

CONSIDER EPILEPSY SURGERY

REFER TO THE CLOSEST EPILEPSY CENTER



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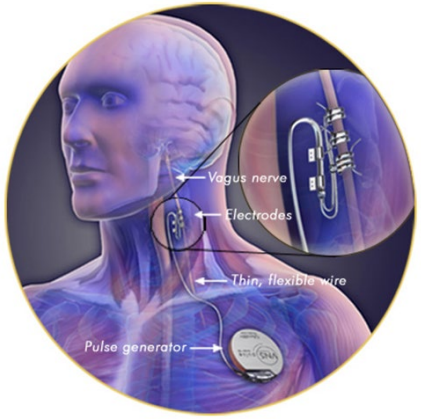
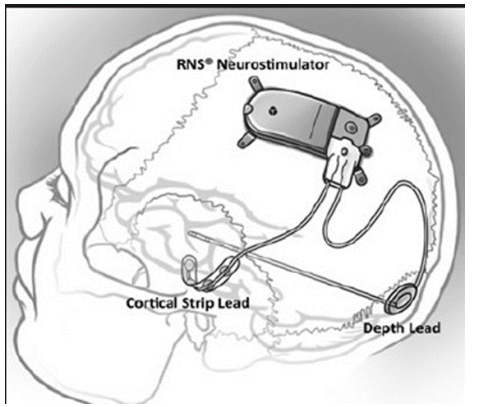
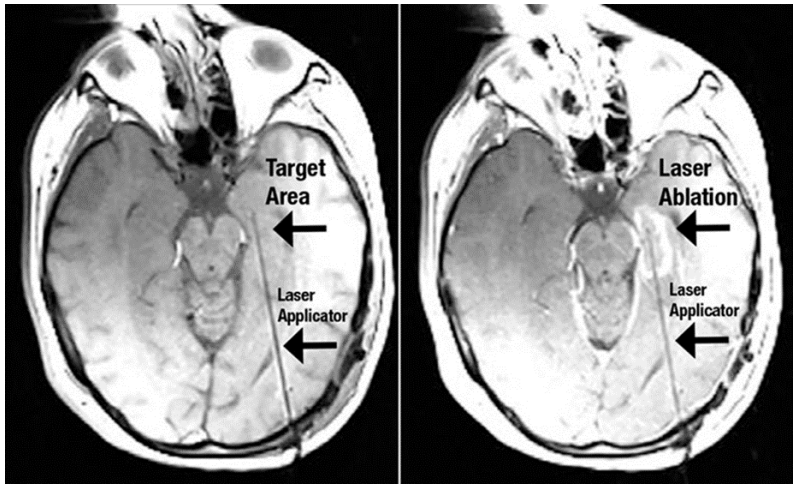
Types of surgeries





- Resection – removal of a lesion or part of the lobe
- Ablation – either laser ablation, stereotactic radiosurgery or thermo-frequency anticoagulation
- Disconnection Procedures – callosotomy, hemispherotomy
- Neuromodulation- VNS, RNS, DBS
- Combination (Resection + Neuromodulation)



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Diets for seizure control

- Ketogenic diet : Oldest anti-epileptic treatment by fasting (starvation ketosis)
- Most appropriate in children, adults least compliant

- Modified Atkins Diet : Less beneficial than ketogenic diet

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COMORBIDITIES WITH EPILEPSY

Psychiatric:

- Depression (35%) and anxiety (19%)
- Suicide risk 25 times more than in general population
- Psychosis (7%)
- 2008 meta-analysis found a 1.8-fold increased risk of suicidality associated with ASMs

Cognitive

- Higher prevalence of impaired cognition compared to age-education matched healthy individuals

Mortality

- Risk of Sudden Unexpected Death in Epilepsy (SUDEP)
- 1.2/1000 patient years in adults
- Main risk factor: poorly controlled GTC seizures

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Functional restrictions that impact Quality of Life (QOL)

Driving:

- Privilege and not a right
- # 1 reason that impacts QOL
- Restrictions vary by state, only 6 states have mandatory physician reporting laws (CA, DE, NV, NJ, OR, PA)

Occupation:

- Airline pilot
- Armed forces
- CDL license- interstate 18-wheeler truck drivers
- Barriers to employment- Heavy machinery, sharp objects, open flames
- Odd work hours

Take Home Points- Management

- Obtain a good history for a proper seizure classification
- Start epilepsy work up- EEG and MRI
- Start ASM if recurrence risk is high
- Be mindful of ASM side effects, pertinent labs, DEXA scan
- Refer to a neurologist/ closest epilepsy center if patient has seizures
- Assess for depression/ anxiety/ suicide in patients with epilepsy
- Counsel about long term cognitive problems with poorly controlled epilepsy