NOVEL TRENDS IN EPILEPSY MANAGEMENT

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Disclosures

- No conflicting interests

OBJECTIVES

- Diagnosing epileptic disorder
- Advancement in diagnostic tools
- Available medical treatments- older and new ones
- Understanding surgical options
- Non-medicinal treatments

Question 1

- A 54 year old female admitted to hospital with new onset generalized tonic clonic seizure. This happened after a night of sleep deprivation when she was out with her friends for drinks. Patient was given Levetiracetam in ER and was continued during hospitalization. EEG is normal. MRI brain without any abnormalities. She denies having any passing out spells, confusional events and seizure like spells in the past. There is no family history of seizures. What will be the best course of action at time of discharge.
- A- Stop Levetiracetam, seizure education and follow up in clinic
- B-Continue Levetiracetam and followup in clinic
- C- Stop Levetiracetam and start Oxcarbazepine
- D-Refer to surgery for possible VNS evaluation

Question 2

- 33 year od female with history of seizures since age 26 is admitted with status epilepticus. Home medications include Levetiracetam, Lacosamide and Oxcarbazepine and despite taking them on regular basis, she is having 3-4 seizures per week. She had a prolonged hospitalization and was placed on phenobarbital coma to break the status epilepticus. At the time of discharge, she is on Lacosamide, Oxcarbazepine, Phenobarbital and valproic acid. EEG showed right temporal epileptiform discharges. Soon after her discharge, you receive a call from her husband that she is still having 1-2 seizures per week. What should be your best course of action
- A. Add 5^{th} seizure medication
- B. Refer for evaluation for VNS
- C. Refer her for surgical evaluation
- B or C are both acceptable options

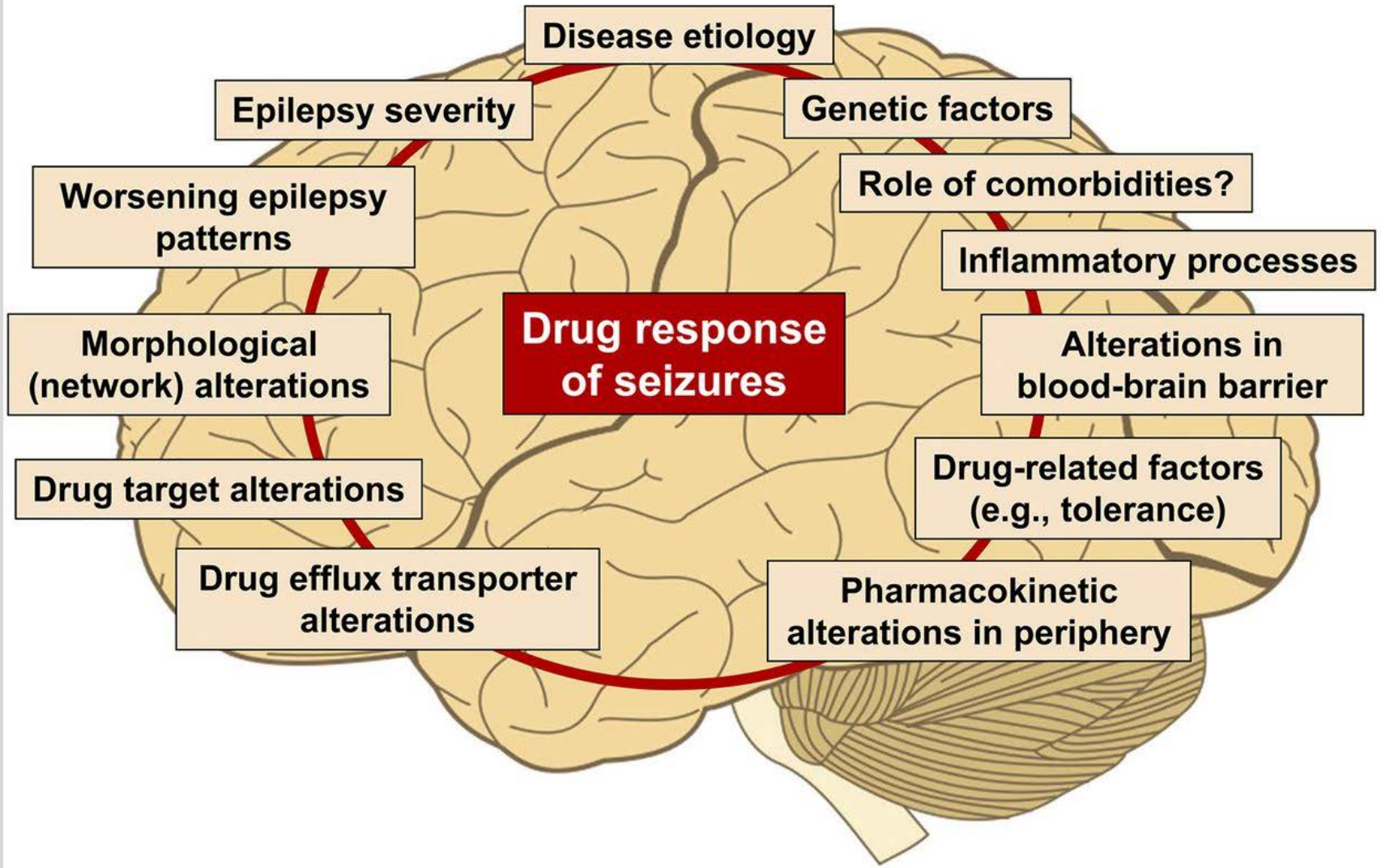
Question 3

- A 3 year old boy starts having frequent seizures. He has been tried on multiple seizure medications. All of them work for few weeks to reduce the seizures but then start losing effect. He has been given ACTH and steroids at one point as well but no significant improvement was noticed. Father is interested in alternative management of this childs epilepsy and would like to try non-surgical and non-medicinal treatment option. What would be the best course of action
- A- Tell the father that there is nothing like this and he needs to see another neurologist
- B- Refer to a dietician for ketogenic diet education
- C- Refer for evaluation of Vagus nerve stimulus
- D-Give him another seizure medication and see if that works

A LITTLE ABOUT SEIZURE AND EPILEPSY

- Definition
- Difference between the two
- Why is it important to know the difference

Potential mechanisms of drug resistance in epilepsy



Consequences of Intractable Epilepsy

- Shortened Life span
  - SUDEP (2-18% of death in epileptics)
  - Bodily Injury
  - Status epilepticus
- Neuropsychological and psychiatric impairment
  - Depression
  - Reduced quality of Life
- Social Disability
  - Reduced marriage rates
  - Reduced employment rates

ADVANCEMENT IN DIAGNOSTIC TOOLS

Diagnostic Workup

- Workup depends upon few things
  - HISTORY
    - Family history, trauma, semiology of seizure, previous events etc
  - AGE
    - Seizures common in early and late age with different etiologies
  - COMORBIDITIES
    - Certain habits, medical conditions, certain medications can lead to seizures

- Common workup
  - Common labs- CBC, CMP, thyroid issues
  - CT head
  - MRI head
  - EEG

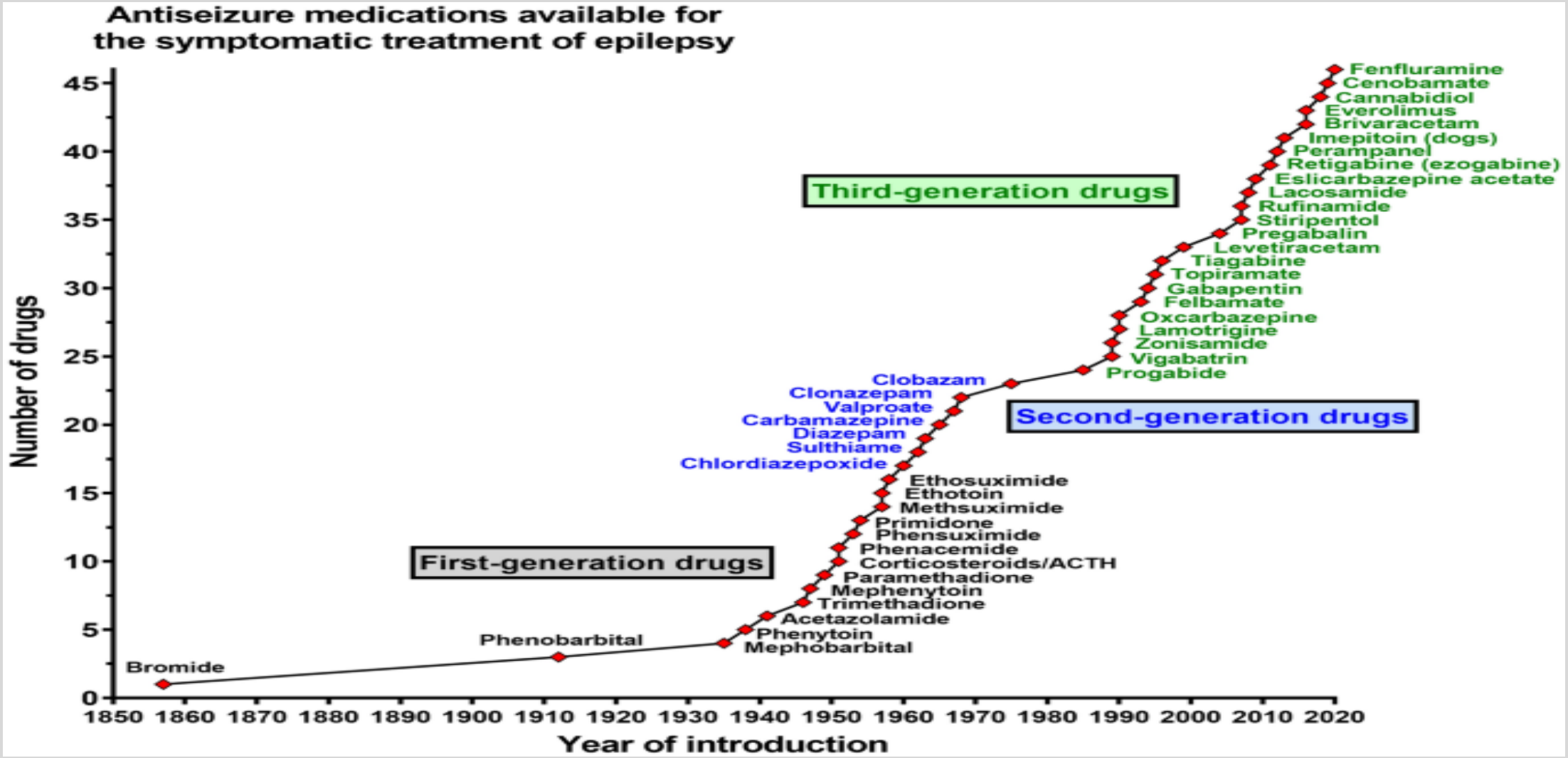
Diagnostic Workup

- Advanced testing
  - Video EEG monitoring
  - Invasive EEG monitoring
  - SPECT Scan (Ictal/Interictal)
  - PET Scan (for highly specialized cases)
  - High resolution MRI Brain
  - Lumbar puncture
  - Magnetoencephalography (MEG) –recording of magnetic fields generated by intraneuronal electrical currents
  - Magnetic Source Imaging (MSI) – combination of MEG source localization with anatomic imaging (MRI), in which the magnetic dipole representing an epileptiform discharge is placed on the patient's MRI scan
  - Electrical Source Imaging (ESI)- integrates spatial and temporal components of EEG

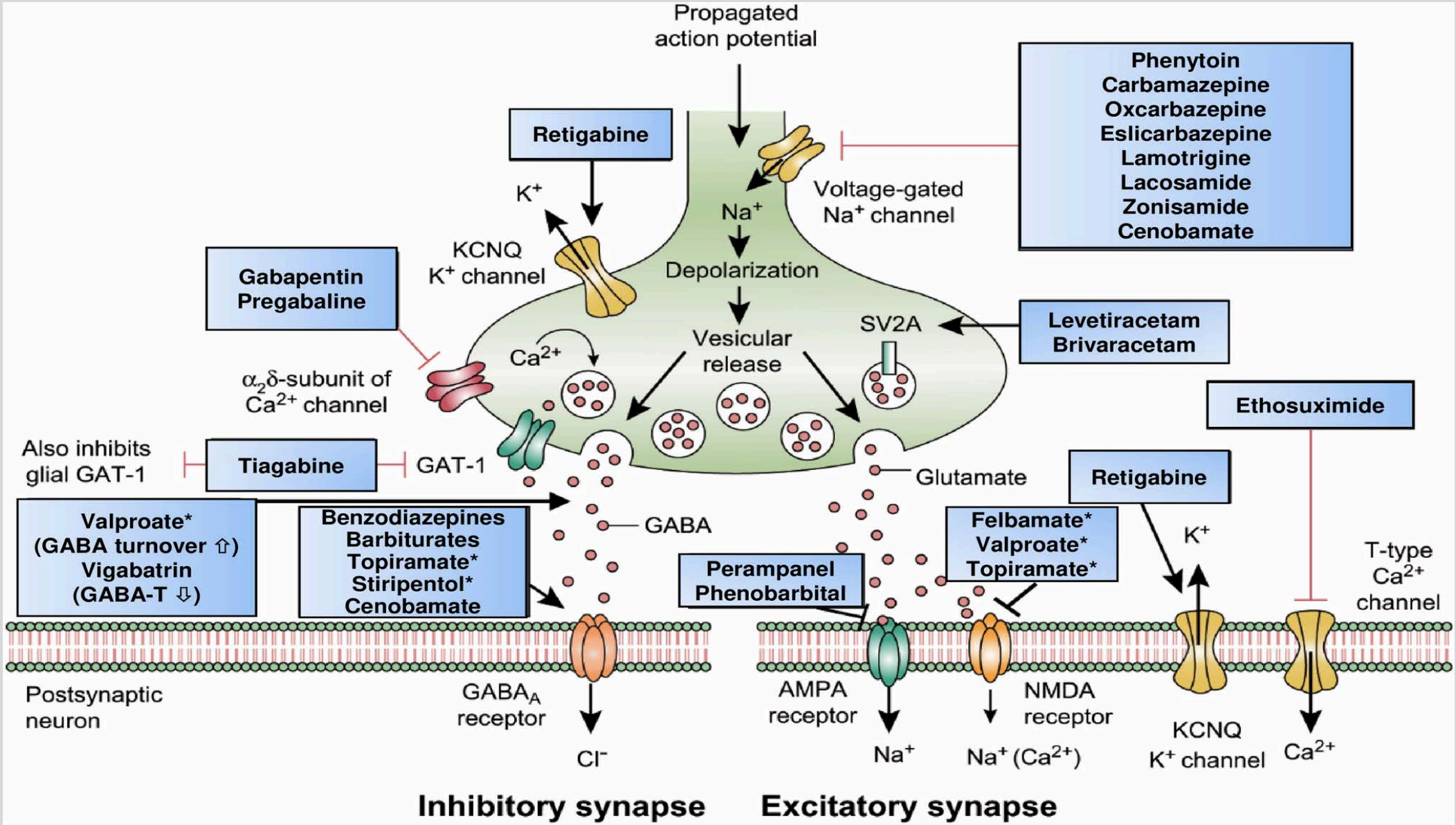
Diagnostic Workup

- Diagnosis in children
  - Detailed history
  - All regular workup
  - Specialized workup including workup for inborn errors of metabolism

AVAILABLE MEDICAL TREATMENTS- OLDER AND NEW ONES



Modified from Löscher and Schmidt [11]. For further details, see Löscher et al. [30]. *ACTH* adrenocorticotropic hormone


Propagated action potential
Retigabine
K+
KCNQ K+ channel
Na+
Voltage-gated Na+ channel
Phenytoin
Carbamazepine
Oxcarbazepine
Eslicarbazepine
Lamotrigine
Lacosamide
Zonisamide
Cenobamate
Depolarization
Gabapentin
Pregabaline
Ca2+
Vesicular release
SV2A
Levetiracetam
Brivaracetam
α2δ-subunit of Ca2+ channel
Ethosuximide
Also inhibits glial GAT-1
Tiagabine
GAT-1
Glutamate
Retigabine
Valproate*
(GABA turnover ⇧)
Vigabatrin
(GABA-T ⇩)
Benzodiazepines
Barbiturates
Topiramate*
Stiripentol*
Cenobamate
GABA
Felbamate*
Valproate*
Topiramate*
K+
Perampanel
Phenobarbital
T-type Ca2+ channel
Postsynaptic neuron
GABAA receptor
AMPA receptor
NMDA receptor
KCNQ K+ channel
Cl-
Na+
Na+ (Ca2+)
Ca2+
Inhibitory synapse
Excitatory synapse

NON-MEDICINAL TREATMENTS

EPILEPSY SURGERY

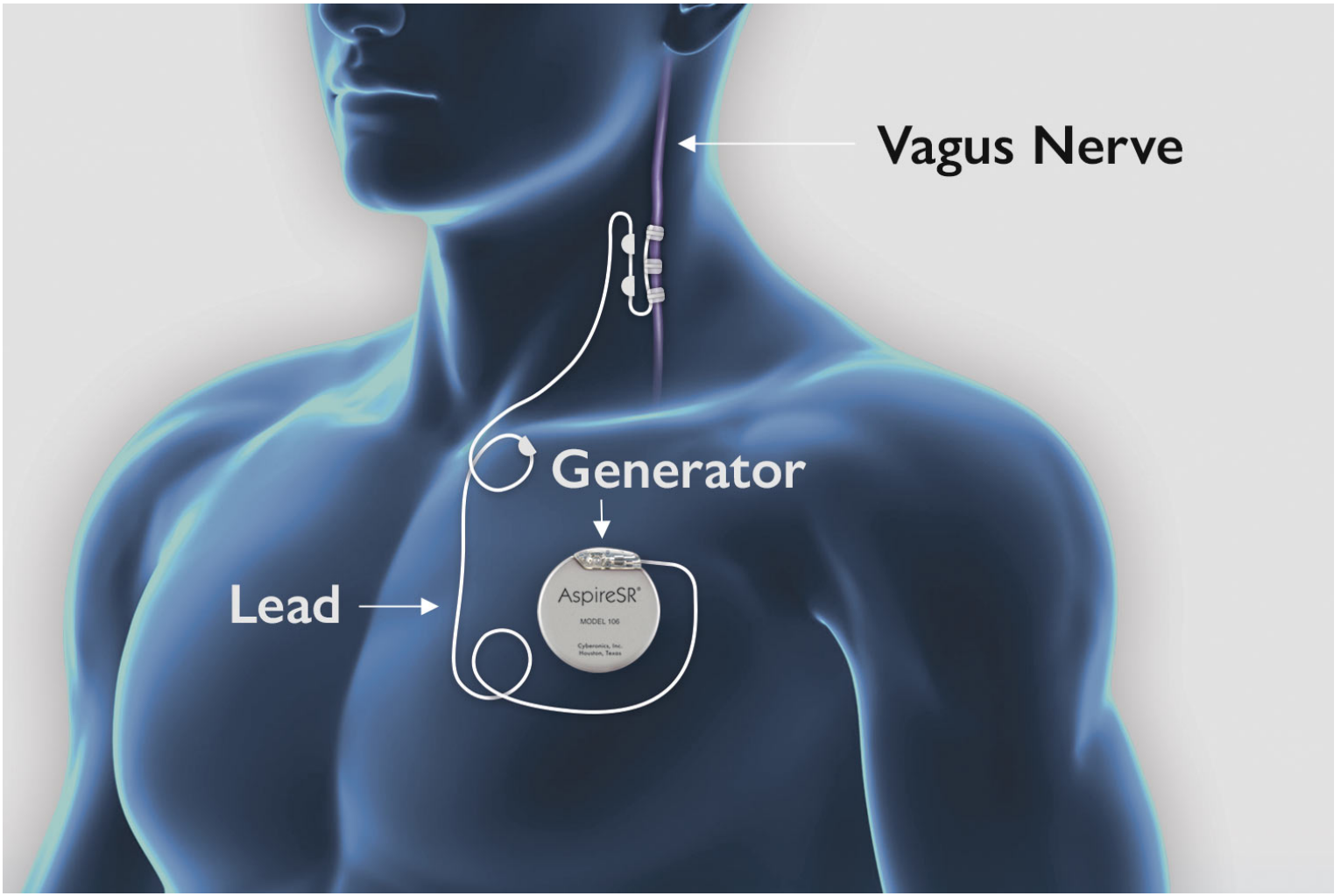
Epilepsy Surgery

- Reserved for patients with medically intractable partial epilepsy
- Surgically remediable epilepsies
  - Temporal lobe epilepsy (80% seizure freedom rate)
  - Lesional epilepsy (around 30-50% seizure freedom)
    - Brain tumors, AVMs, Cavernomas, Hemangiomas, Cortical dysplasias etc
- Epilepsy surgery in children
  - Corpus callosotomy (multiple type of seizures, Lennox gastaut syndrome)
  - Hemispherectomy (perinatal stroke, hemimegalencephaly, multilobar cortical dysplasia, Rasmussen encephalitis, and Sturge-Weber syndrome).

NEUROSTIMULATION

VAGUS NERVE STIMULATION

- Vagus nerve stimulation (VNS) was the first approved therapy utilizing chronic stimulation, FDA approval



VAGUS NERVE STIMULATION

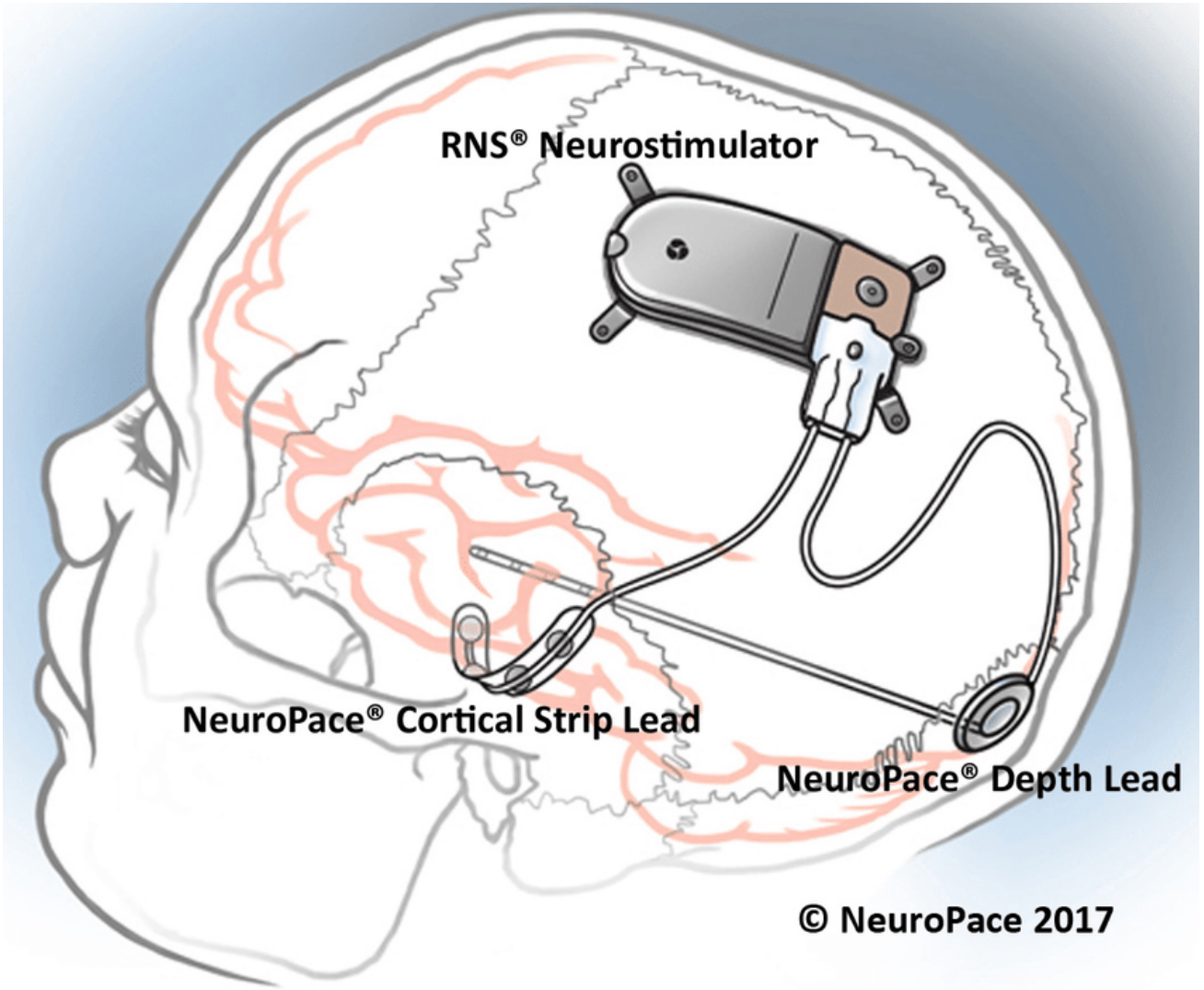
- Actual mechanism of VNS is not established.
- Studies of changes in regional cerebral blood flow with PET during VNS therapy revealed changes in bilateral thalamic regions that correlated with efficacy
- Approval of VNS therapy: E03 (114 pts) E05 (199 pts)
- Two randomized arms:
  - High stimulation: (≤3.5 mA, 30 Hz, pulse width 500 μS, 30s on, 5 min off
  - Low stimulation: (≤3.5mA,1 Hz, 130 μS, 30s on, 180 min off.
- EO3
  - High stimulation group: 24.5% mean reduction in seizures
  - Low stimulation group: 6.1% mean reduction in seizures
  - Responder rate: 27%
- EO5
  - High stimulation group: 27.9% mean reduction in seizure
  - Low stimulation group:15.2% mean reduction in seizure
  - Responder rate: 34%

DEEP BRAIN STIMULATION

DEEP BRAIN STIMULATION

- SANTE Trial
  - Multicentral blinded trial of anterior thalamic stimulation
  - N= 110 pts
  - Refractory partial epilepsy patients
    - 54% had previous epilepsy surgery/VNS
  - 3 month blinded:
  - Significant 38% reduction vs 14.5% in placebo group.
  - Both CPS and SGTC significantly improved with stimulation during the blinded period.
  - TLE Patients (33) 44% reduction in seizure frequency during blinded period vs 22% reduction in seizure frequency in TLE control patients (29, $p = 0.025$).
  - Like other neurostimulation, the efficacy of DBS increased over time in the open label period
    - 41% median seizure frequency drop at 13 months
    - 56% at 2 years
    - 67 at 3 years
  - Anterior thalamic stimulation safe
  - No symptomatic hemorrhages or death.
  - Trend of possible worsening of depression or memory, not confirmed by objective testing.

RESPONSIVE NEUROSTIMULATION



RESPONSIVE NEUROSTIMULATION

- Principle: seizures are self-limited and early intervention can result in reduced seizure duration.
- Closed loop therapy responds shortly after seizure onset to provide therapy for early seizure termination before the seizure evolves to a disabling seizure (e.g. with altered consciousness).
- Multi-center, double-blind, randomized controlled
  - N=191 pts
  - Drug resistant partial epilepsy with one or two seizure foci
  - 32% had previous epilepsy surgery, 34% had prior VNS.
  - Primary outcome: seizure reduction.
  - Blinded phase 12 weeks:
    - 38% reduction vs 17% (p=0.012)
  - Open label period: sham group experience seizure reduction seen in those initially receiving treatment.
  - Progressive improvement with time median seizure reduction ~50% after two years.
- Retention rate of >90% at 3 years
- High retention rates reflect patient satisfaction with the overall response and side effect profile.
- Brief stimulus duration
- A novel type of cortical stimulation is currently being evaluated by using chronic subthreshold stimulation. Good initial results

KETOGENIC DIET

KETOGENIC DIET

- Classic Ketogenic diet
  - High-fat, adequate-protein (1 gram/kg), low-carbohydrate diet
  - Seizure reduction- 60% had more than 50% responder rate and 30 % had more than 90% responder rate
- Modified Atkins diet (easier for adults)
  - 45% had more than 50% reduction in seizures; 25 % had more than 90% reduction==more efficacious in children
- Low glycemic index treatment
  - Only eat food with low glycemic index (<55). Less efficacious
- Medium-chain triglyceride diet.
  - Comparable to classic ketogenic diet

KETOGENIC DIET

- Proposed Mechanism
  - High-fat, adequate-protein low-carbohydrate diet-Starvation state
  - Changes in plasma ketones, insulin, glucose, glucagon, and free fatty acids
  - Results in improvement in seizure frequency
  - Mechanism is likely multifactorial
  - Increased mitochondrial biogenesis, oxidative phosphorylation, enhanced GABA levels, reduced neuronal excitability and firing, and stabilized synaptic function

CANNABANOIDS

CANNABANOIDS

- Unknown mechanism but possibly inhibits catalytic activity of CYP3A4 and CYP3A5 as well as CYP2AC enzyme
- Cannabidiol is FDA approved for Dravet syndrome and Lennox-Gastaut syndrome
- Modest efficacy in trials
- Smoking marijuana???

Question 1

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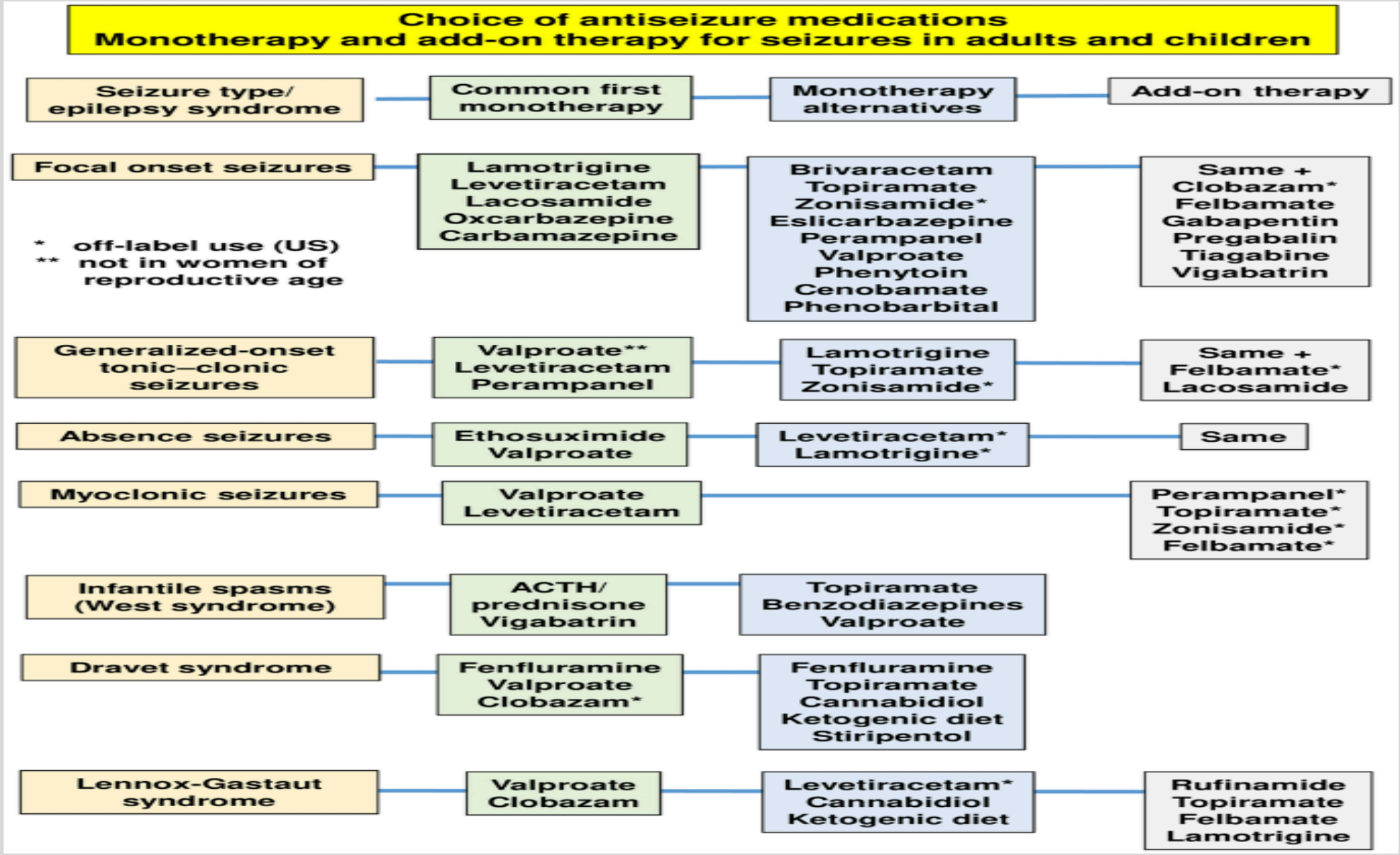
Choice of antiseizure medications
Monotherapy and add-on therapy for seizures in adults and children
Seizure type/ epilepsy syndrome
Common first monotherapy
Monotherapy alternatives
Add-on therapy
Focal onset seizures
Lamotrigine
Levetiracetam
Lacosamide
Oxcarbazepine
Carbamazepine
Brivaracetam
Topiramate
Zonisamide*
Eslicarbazepine
Perampanel
Valproate
Phenytoin
Cenobamate
Phenobarbital
Same +
Clobazam*
Felbamate
Gabapentin
Pregabalin
Tiagabine
Vigabatrin
* off-label use (US)
** not in women of reproductive age
Generalized-onset tonic–clonic seizures
Valproate**
Levetiracetam
Perampanel
Lamotrigine
Topiramate
Zonisamide*
Same +
Felbamate*
Lacosamide
Absence seizures
Ethosuximide
Valproate
Levetiracetam*
Lamotrigine*
Same
Myoclonic seizures
Valproate
Levetiracetam
Perampanel*
Topiramate*
Zonisamide*
Felbamate*
Infantile spasms (West syndrome)
ACTH/ prednisone
Vigabatrin
Topiramate
Benzodiazepines
Valproate
Dravet syndrome
Fenfluramine
Valproate
Clobazam*
Fenfluramine
Topiramate
Cannabidiol
Ketogenic diet
Stiripentol
Lennox-Gastaut syndrome
Valproate
Clobazam
Levetiracetam*
Cannabidiol
Ketogenic diet
Rufinamide
Topiramate
Felbamate
Lamotrigine

TABLE. ANTISEIZURE MEDICATIONS

Drug (Trade names)	Mechanism of action	Dose	Drug formulation	Adverse events (common)	Clinical pearls
Brivaracetam[a] (Briviact)	Binds to synaptic vesicle protein 2A (SV2A)	Initial dose: 50 mg twice daily Maximum dose: 100 mg twice daily (200 mg twice daily in status epilepticus)	Solution, oral: 10 mg/mL (300 mL) Solution, injection: 50 mg/5 mL Tablet: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg	CNS: dizziness, somnolence GI: nausea/vomiting Other: fatigue	Not recommended for end-stage renal disease on dialysis Adjust dose in hepatic impairment Tablets cannot be crushed, recommend solution if unable to swallow whole
Cannabidiol[a] (Epidiolex)	Unknown	Initial dose: 2.5 mg/kg twice daily, titrate weekly Maximum dose: 20 mg/kg/day	Solution, oral: 100 mg/mL (100 mL bottle), strawberry flavored	CNS: drowsiness, lethargy, sedation GI: decrease appetite Hematologic: anemia Hepatic: increased ALT, AST	Obtain baseline ALT, AST, total bilirubin prior to treatment Specialty pharmacy only High-fat or high calorie meals, increases absorbtion; taking consistently in fasted or fed state is recommended
Clobazam[b] (Onfi) Clobazam film[b] (Sympazan)	Binds to $GABA_A$ receptors	Initial dose: 5 mg twice daily, titrate weekly Maximum dose: 20 mg twice daily (40 mg twice daily for refractory seizures)	Film, oral: 5 mg, 10 mg, 20 mg Suspension, oral: 2.5 mg/mL (120 mL), contains propylene glycol[c] Tablet, oral: 10 mg, 20 mg	CNS: drowsiness, lethargy, irritability, aggressive behavior Respiratory: upper respiratory tract infection Miscellaneous: fever	Black box warning: avoid use with benzodiazepines and opioids-may cause sedation and respiratory depression Use with caution in patients with history of drug abuse or alcoholism Dose adjustment needed for hepatic impairment Metabolized via CYP3A4
Eslicarbazepine acetate (Aptiom)	Inhibits voltage-gated sodium channels	Initial dose: 400 mg daily, titrate weekly Maximum dose: 1,600 mg daily	Tablet, oral: 200 mg, 400 mg, 600 mg, 800 mg	CNS: dizziness, drowsiness, headache GI: nausea Ophthalmic: diplopia	Concomitant use with oxcarbazepine is not recommended Dose adjustment is needed when taken with other enzyme-inducing drugs (eg, phenytoin, phenobarbital, or primidone)
Lacosamide[a] (Vimpat)	Enhances slow-inactivation of voltage-gated sodium channels	Initial dose: 50 mg twice daily (100 mg twice daily if monotherapy) Maximum dose; 200 mg twice daily (300 mg twice daily for refractory status epilepticus)	Solution, intravenous (preservative free): 200 mg/20 mL (20 mL vial) Solution, oral: 10 mg/mL (200 mL, 456 mL, contains propylene glycol[c]) Tablet, oral: 50 mg, 100 mg, 150 mg, 200 mg	CNS: dizziness, headache GI: nausea	Monitor ECG, may prolong P-R interval Concominant use with phenytoin requires more frequent cardiac monitoring and may require dose adjustment Recommend to adjust dose in hepatic and renal impairment Metabolized via CYP3A4, CYP2C9 and CYP2C19
Oxcarbazepine (Trileptal)	Active metabolite induces blockade of voltage-sensitive sodium channels	Immediate release: 300 mg twice daily, titrate up to 600 mg twice daily Extended release: 600 mg once daily, titrate weekly up to 2,400 mg daily	Suspension,oral: 300 mg/5mL (250 mL), contains propylene glycol[c] Tablet, oral: 150 mg, 300 mg, 600 mg Tablet, extended-release (XR): 150 mg, 300 mg, 600 mg	CNS: dizziness, drowsiness, headache GI: vomiting, nausea, abdominal pain Ophthalmic: diplopia, nystagmus	May cause hyponatremia, recommend to monitor sodium level if patient develops impaired consciousness, nausea, malaise, seizures May cause hypothyroidism Special populations: consider screening for HLA allele*B 1502 in people of Asian descent Extensively metabolized in the liver to its active metabolite 10-monohydroxy metabolite
Perampanel[d] (Fycompa)	AMPA glutamate receptor antagonist	With enzyme-inducing medications (eg, phenytoin, carbamazepine, or oxcarbazepine): Initial dose: 4 mg at bedtime Maximum dose: 12 mg at bedtime Without enzme-inducing medications: Initial dose: 2 mg at bedtime, titrate weekly Maximum dose 12 mg at bedtime	Suspension, oral: 0.5 mg/mL (340 mL) Tablet, oral: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg	CNS: dizziness, vertigo, drowsiness, hostility, aggressive behavior Endocrine: weight gain GI: vomiting, nausea, abdominal pain	Black box warning: may cause serious psychiatric and behavioral reactions Metabolized by CYP3A4/5 Highly protein bound to albumin-monitor side effects if albumin is low
Rufinamide (Banzel)	Modulates sodium channels via prolongation of inactive state	Initial dose: 200-400 mg twice daily Maximum dose: 1600 mg twice daily If patient is on valproate: start at less than 400 mg/day	Suspension, oral: 40 mg/mL (460 mL), contains propylene glycol[c] Tablet, oral: 200 mg, 400 mg	Cardiovascular: shortened QT interval CNS: headache, drowsiness, dizziness GI: vomiting, nausea	Not recommended for severe hepatic impairments Many drug-interactions Monitor for suicidal ideation Population pharmacokinetics showed that women have decrease drug clearance compared with men
Tiagabine hydrochloride (Gabitril)	Inhibits GABA uptake into the presynaptic neurons	With enzyme- inducing medication: 4 mg daily, titrate weekly Without enzyme-inducing medication: recommend starting at a lower dose and titrate slowly Maximum dose: 56 mg/day in 2-4 divided doses	Tablet, oral: 2 mg, 4 mg, 12 mg, 16 mg	CNS: dizziness, drowsiness GI: nausea Neuromuscular: weakness, tremor	Possible ophthalmic side effects Check for drug-drug interactions Metabolized via CYP 3A4 enzymes Highly protein-bound to albumin and alpha-1 acid glycoprotein
Vigabatrin (Sabril)	Irreversible inhibitor of GABA aminotransferase	Initial: 500 mg twice daily, titrate weekly Maximum dose: 1.5 g twice daily	Packet, oral: 500 mg (50 each box) Tablet, oral: 500 mg	CNS: drowsiness, headache, fatigue Endocrine/Metabolic: weight gain GI: vomiting, constipation, diarrhea Neuromuscular: tremor Ophthalmic: visual field loss	Considered hazardous agent, use precaution when administering or disposing this medication

Abbreviations: ALT, alanine aminotransferase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AST, aspartate aminotransferase; CNS, central nervous system; CYP, cytochrome P; ECG, electrocardiogram; GI, gastrointestinal.
[a] Schedule V controlled substance; [b] Schedule IV controlled substance; [c] Contains propylene glycol, use caution when using in neonates because of the risk of fatal toxicities such as metabolic acidosis, renal failure, CNS depression and seizures; [d] Schedule III controlled substance.