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Update on Epilepsy - Newer Treatment Options

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Update On Epilepsy The Newer Treatment Options

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Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation.

Objectives

- Describe current treatment strategies for epilepsy
- Introduce new treatment options for epilepsy
- Discuss the impact of legislation on patient access to these new therapies

What is a Seizure?

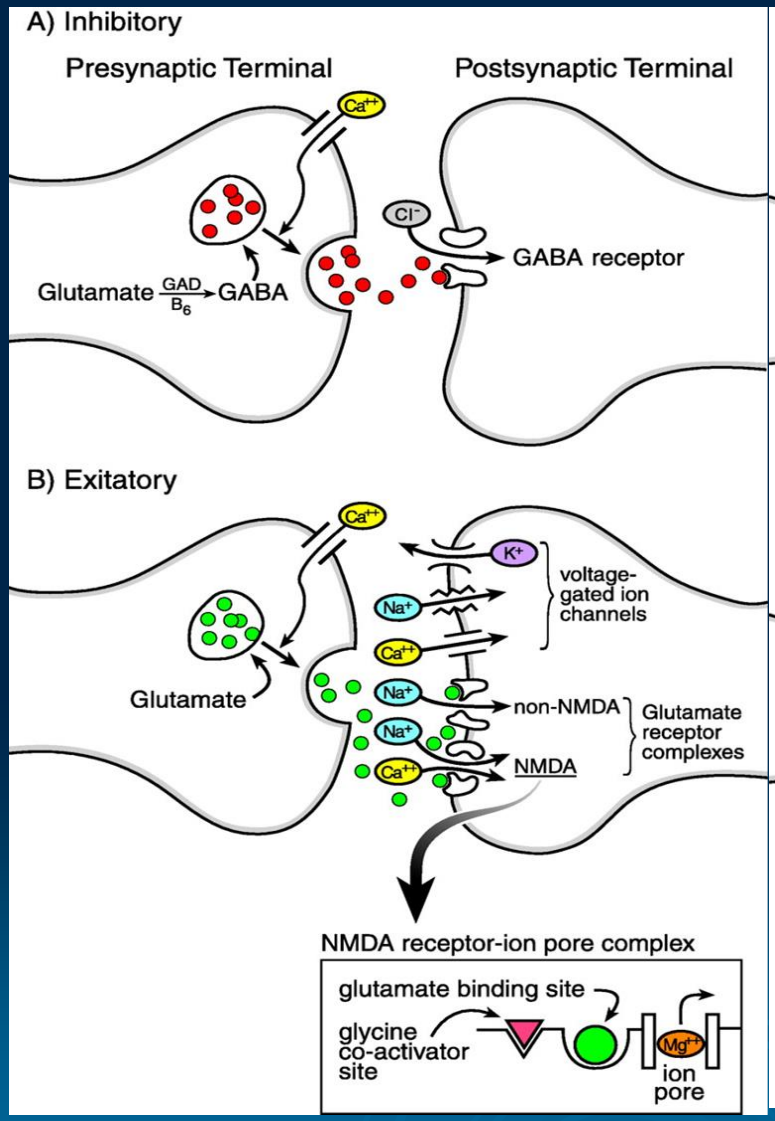
- A seizure occurs when brain cells misfire and stop working the way they are supposed to, sending too many electrical signals at one time
- These uncontrolled electrical signals cause a change in awareness, movement or sensation

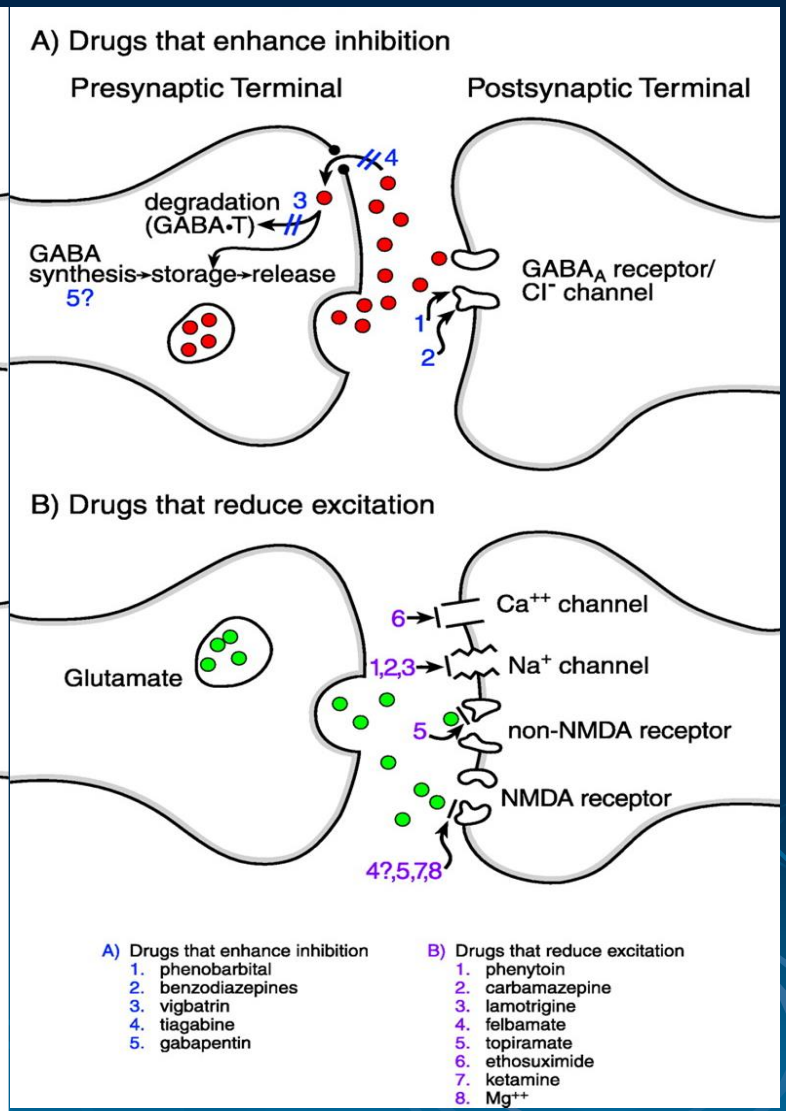
Pathophysiology

- Excitation through glutamate
- Inhibition through gamma-Aminobutyric acid (GABA)

Source: http://pedsinreview.aappublications.org/content/pedsinreview/19/10/342/F2.large

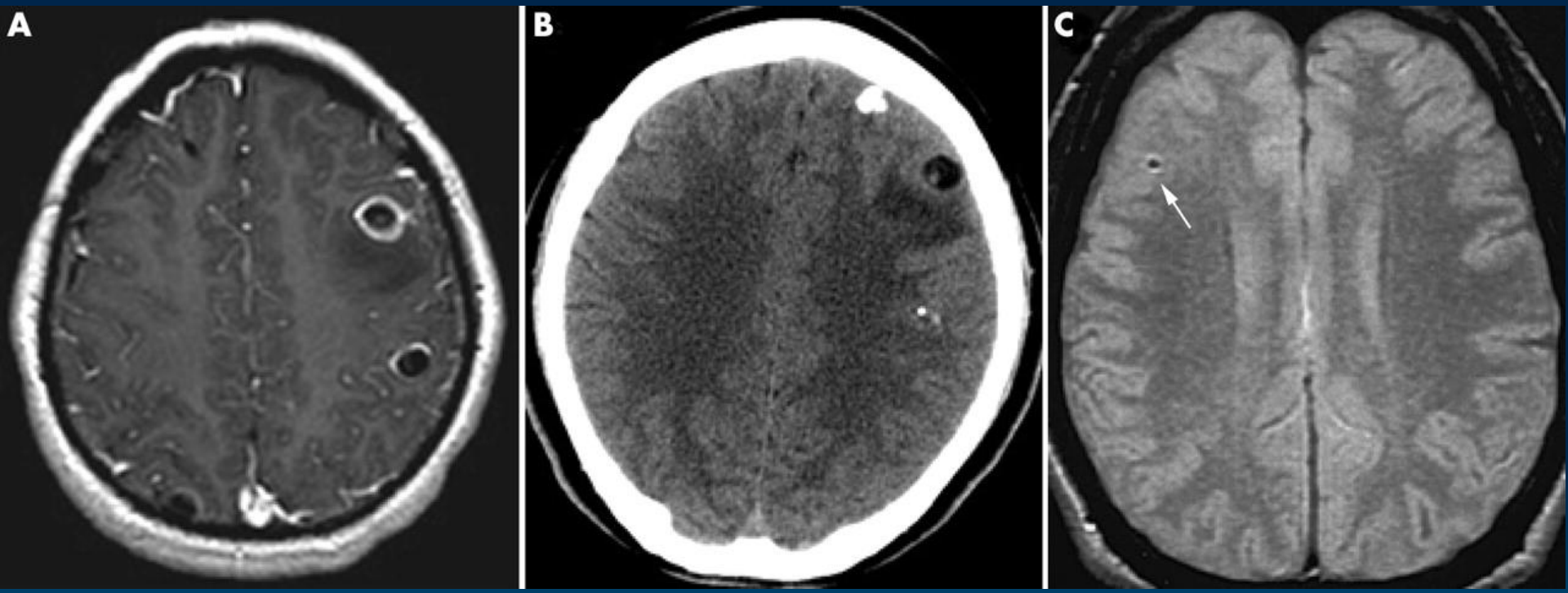
Pathophysiology





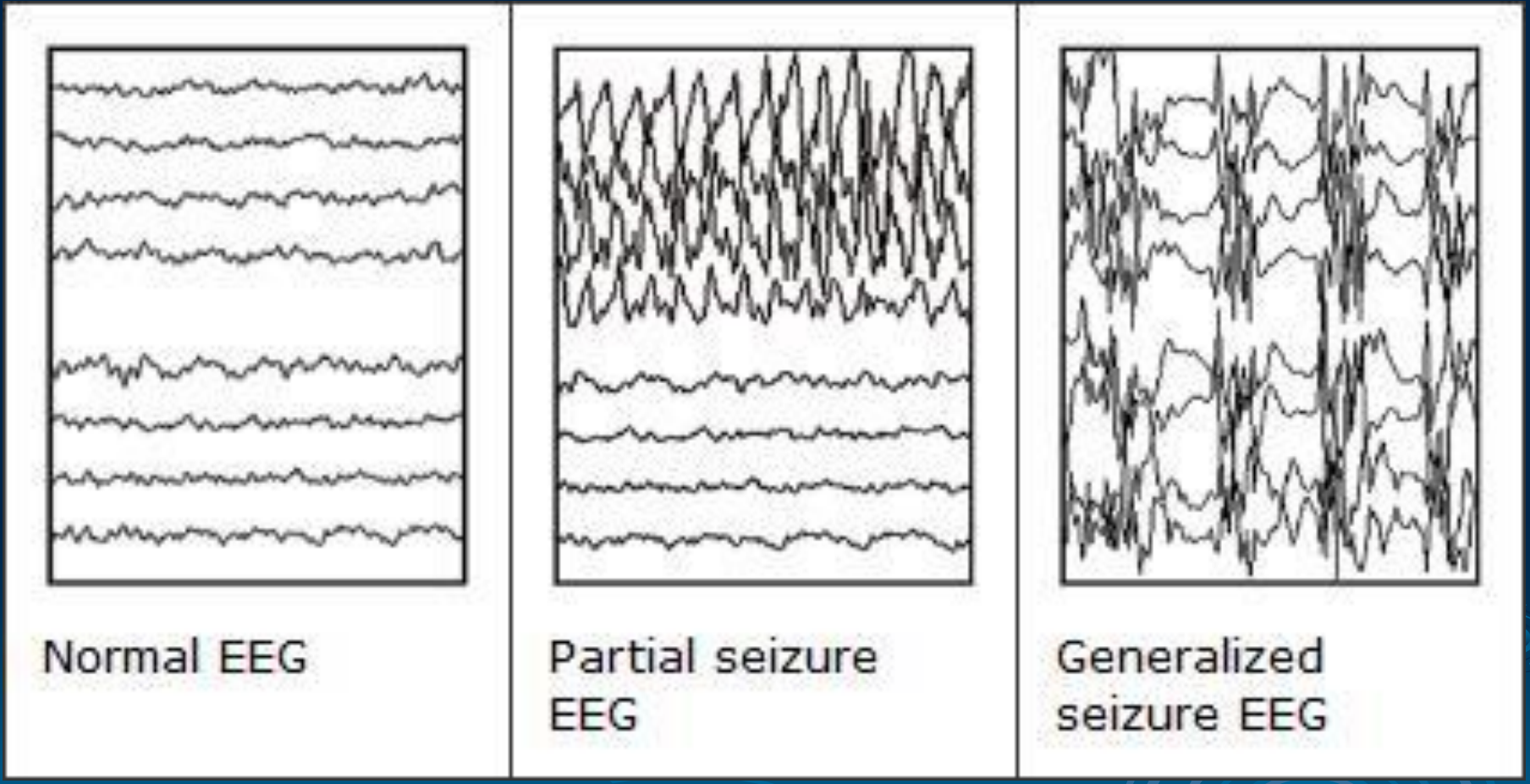
Source: http://pedsinreview.aappublications.org/content/pedsinreview/19/10/342/F2.large.jpg
http://pedsinreview.aappublications.org/content/pedsinreview/19/10/342/F6.large.jpg

Diagnosis of Seizures



Source: https://jnnp.bmj.com/content/jnnp/76/suppl_3/iii2/F5.large.jpg

Diagnosis of Seizures



Source: https://www.mountnittany.org/assets/images/krames/Image_201608102119_205.jpg

What is Epilepsy?

- At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an epilepsy syndrome

Facts About Epilepsy

- Causes: head injuries, infections, strokes, birth defects, and brain tumors
- ~50 million people worldwide have epilepsy
- 2.4 million people are newly diagnosed each year
- ~70% of people respond to treatment
- Epilepsy is not hereditary, but genetics sometimes plays a role

World Health Organization

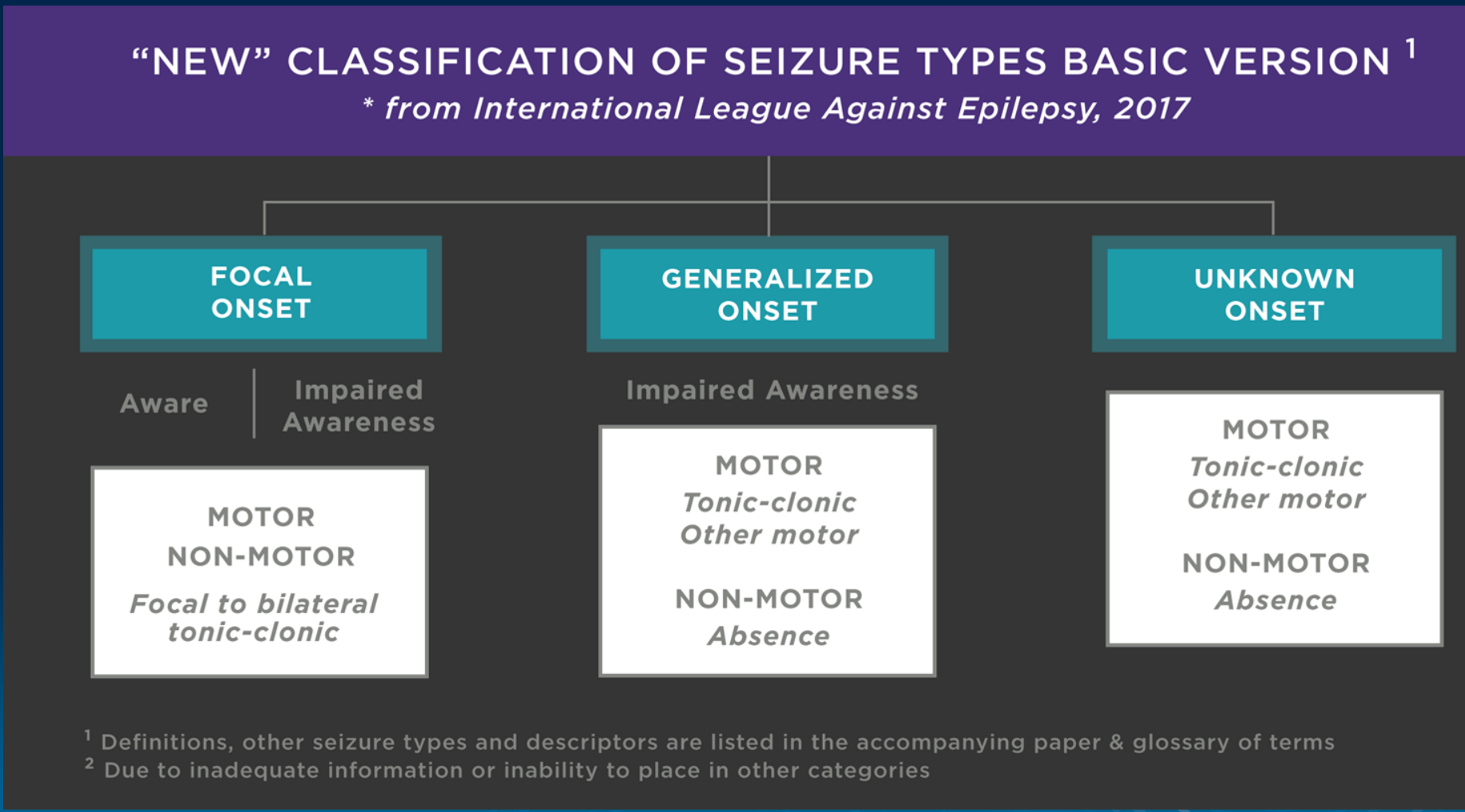
A few known people with Epilepsy

- Julius Caesar
- Michelangelo
- Ludwig Van Beethoven
- Thomas Edison
- Leonardo Da Vinci
- Charles Dickens
- Edgar Allan Poe
- Adam Horowitz – Beastie Boys
- Amy Lee – Evanescence
- Neil Young
- Jonathan Davis - Korn
- Susan Boyle
- Prince
- Lindsey Buckingham – Fleetwood Mac
- Danny Glover
- Hugo Weaving – Matrix, Lord of the Rings, Captain America
- Dai Greene – Olympian
- Jason Snelling- NFL
- Alan Fonseca- NFL
- John Roberts – Supreme Court Justice
- Melanie Griffith – Actress

Types of Seizures

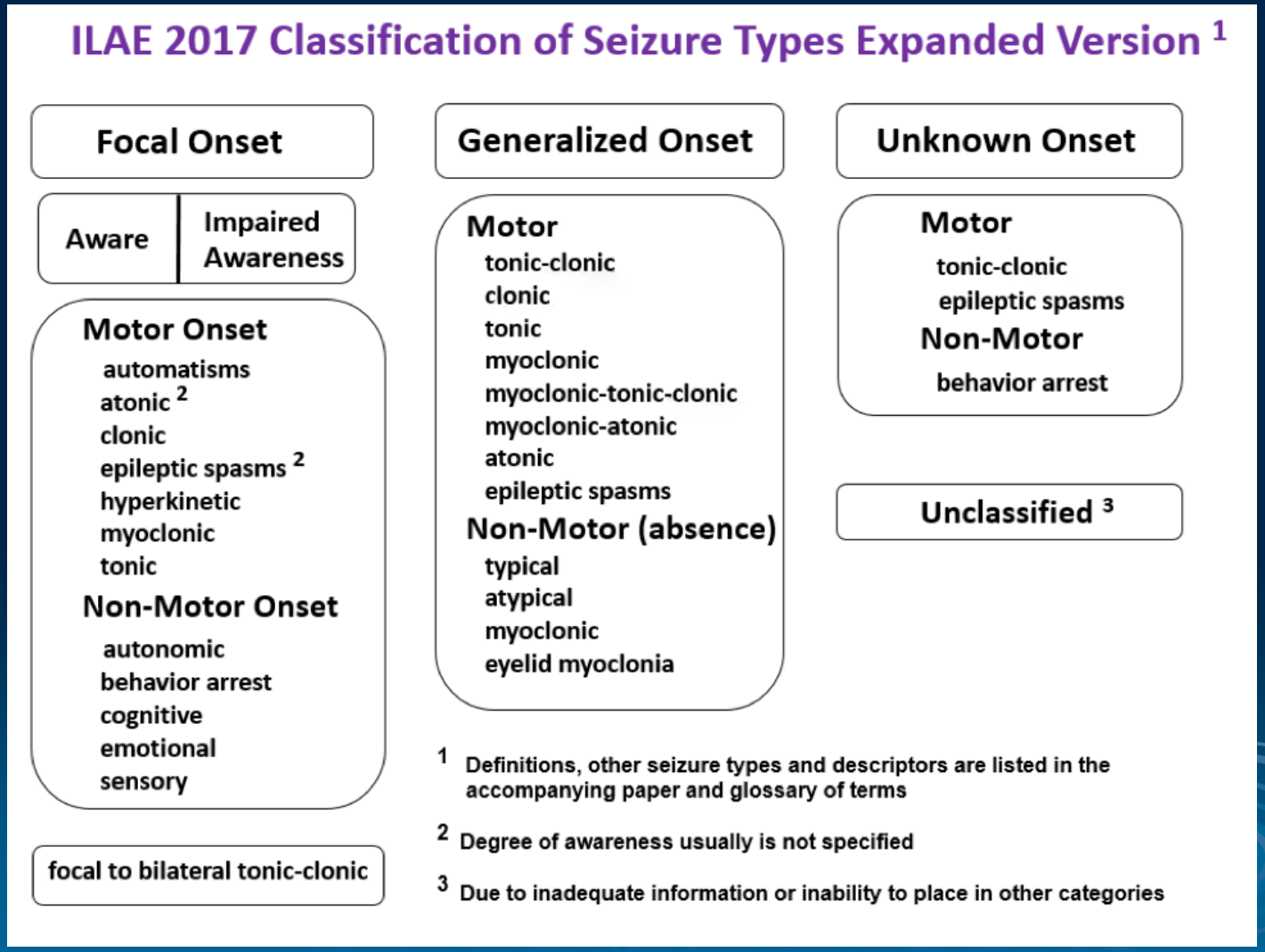
Infantile Spasms	Quick sudden movements that start between 3 months and 2 years of age
Absence Seizures (Petit Mal)	Blank state beginning and ending suddenly with an unresponsive state
Myoclonic Seizures	Sudden, brief, massive muscle jerks
Atonic Seizures	Known as drop attacks, characterized by a sudden collapse and fall
Simple Partial Seizures	Twitching begins in a focal area of the body and may spread, but it cannot be controlled
Complex Partial Seizures	Usually start with a blank state, followed by chewing or other repetitive activity. Patient is unresponsive and unaware
Tonic-Clonic (Grand Mal)	Sudden outburst, patient may fall and become rigid. Patient will either have shallow breathing or temporarily stop breathing. Skin may be flushed, bladder and bowel control may be lost, and patient may lose consciousness

Types of Seizures



Fisher, Robert S., et al. "Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology." Epilepsia 58.4 (2017): 522-530.

Types of Seizures



Fisher, Robert S., et al. "Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology." Epilepsia 58.4 (2017): 522-530.

Timeline of Antiepileptics

1st Generation	1912	Phenobarbital
	1939	Phenytoin
	1953	Carbamazepine
	1958	Ethosuximide
	1963	Sodium Valproate
2nd Generation	1993	Felbamate and Gabapentin
	1994	Lamotrigine
	1996	Topiramate and Tiagabine
	1999	Levetiracetam
	2000	Oxcarbazepine and Zonisamide

Source: Preceden. Accessed from https://www.preceden.com/timelines/28748-epilepsy-timeline on 2018 Dec 11.

Recent Antiepileptics

2005	Pregabalin
2008	Rufinamide
2009	Vigabatrin and Lacosamide
2011	Clobazam
2012	Perampanel
2013	Eslicarbazepine
2016	Brivaracetam
2018	Cannabidiol Solution

Source: Skelton, J B., et al. J. Am. Pharm. Assoc. 2017 vol. 57, no. 4.

Guidelines for Treatment

- Adults with New Onset Epilepsy with Focal Epilepsy or Unclassified Tonic-Clonic Seizures <u>Monotherapy</u>
  - **<u>Lamotrigine</u>** may be considered to decrease seizure frequency (**<u>Level B</u>**)
  - **<u>Leviteracetam and Zonisamide</u>** may be considered to decrease seizure frequency **(<u>Level C</u>)**
  - **<u>Gabapentin</u>** may be considered in patients ≥60 years old to decrease seizure frequency **<u>(Level C)</u>**
  - **<u>Vigabatrin</u>** toxicity profile **precludes** it as 1st line therapy **<u>(Level C)</u>**
  - **<u>Pregabalin</u>** use at 150 mg/day is possibly **<u>less efficacious</u>** than **<u>Lamotrigine</u>** use at 100 mg/day **<u>(Level C)</u>**

Kanner, Andres M., et al. "Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society." *Neurology* (2018): 10-1212.

Guidelines for Treatment

- Recommendation for Childhood Absence Epilepsy
  - Unless there are compelling reasons based on adverse events profile, **ethosuximide** or **valproic acid** use should be considered **before lamotrigine** use to decrease seizure frequency in treating absence seizures in childhood absence epilepsy **(Level B)**

Kanner, Andres M., et al. "Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society." *Neurology* (2018): 10-1212.

Guidelines for Treatment

- Adults with Treatment-Resistant Focal Epilepsy Monotherapy
  - **Eslicarbazepine** use may be considered to decrease seizure frequency as monotherapy **(Level C)**
- Adults and Pediatric Patients with Treatment-Resistant Generalized Epilepsy - Adjunctive
  - IR and ER **lamotrigine** use should be considered as add-on therapy in treating adults with TR generalized tonic-clonic seizures secondary to GE **(Level B)**
  - **Levetiracetam** use should be considered to decrease seizure frequency as add-on therapy for TR GTC seizures and for TR juvenile myoclonic epilepsy

Kanner, Andres M., et al. "Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society." *Neurology* (2018): 10-1212.

Guidelines for Treatment

- Adults with Treatment-Resistant Focal Epilepsy Adjunctive Therapy
  - Immediate-release **pregabalin** and **perampanel** are established as effective to reduce seizure frequency
  - **(Level A)**
  - **Vigabatrin** and **rufinamide** should be considered established as effective for decreasing seizure frequency but are **not first-line agents** (**retinopathy** risk with VGB and modest benefit with RFN) **(Level A)**
  - **Lacosamide**, **eslicarbazepine**, and extended-release **topiramate** use should also be considered to decrease seizure frequency in this population **(Level B)**
  - **Clobazam** and extended-release **oxcarbazepine** use may be considered to decrease seizure frequency **(Level C)**

Kanner, Andres M., et al. "Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society." *Neurology* (2018): 10-1212.

Guidelines for Treatment

- Adults and Pediatric Patients with Lennox-Gastaut Syndrome – Adjunctive Therapy
  - **Rufinamide** use should be considered established as effective as add-on therapy **(Level A)**
  - **Clobazam** should be considered **(Level B)**
- Pediatric Patients with Treatment Resistant Focal Epilepsy – Adjunctive Therapy
  - **Levetiracetam** should be considered **(Level B for ages 1 month to 16 years)**
  - **Zonisamide** use should be considered **(Level B)**
  - **Oxcarbazepine** use should be considered **(Level B)**

Kanner, Andres M., et al. "Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society." *Neurology* (2018): 10-1212.

Principles of AED Selection

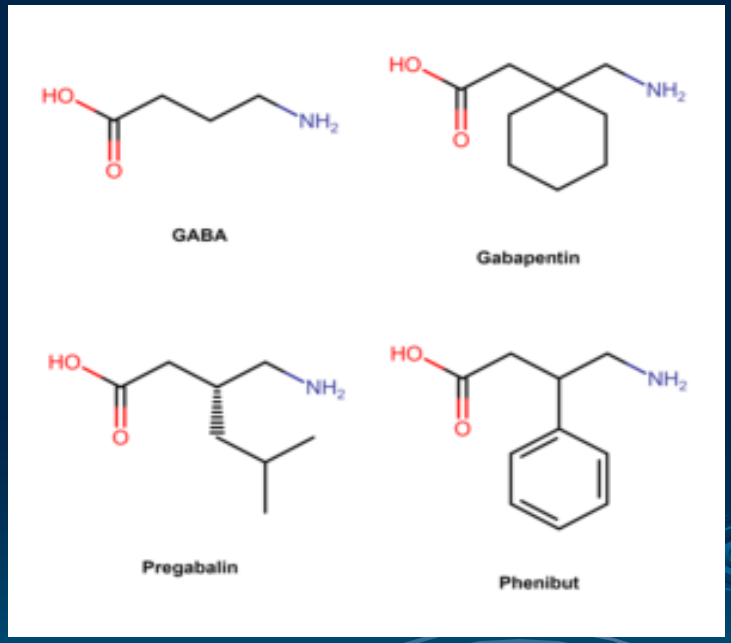
- After a first seizure, a majority of patients are not placed on AEDs
- Medications are first line therapy for treatment
- Patients are started on AED monotherapy and adjunctive therapy is added if treatment fails
- ~60% of patients will respond to the first two AEDs tried
- Medications must be selected based on a number of factors, from type of epilepsy, to factors like patient adherence and insurance coverage

Berg A. (2008). Risk of recurrence after a first unprovoked seizure. Epilepsia 49(Suppl. 1), 13-18. doi: 10.1111/j.1528-1167.2008.01444.x
Krumholz A, et al. (2007). Practice parameter: Evaluating an apparent unprovoked first seizure in adults (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology, 69(21),1996-2007.

Pharmacological Therapy

Pregabalin (pre-gab-a-lin)

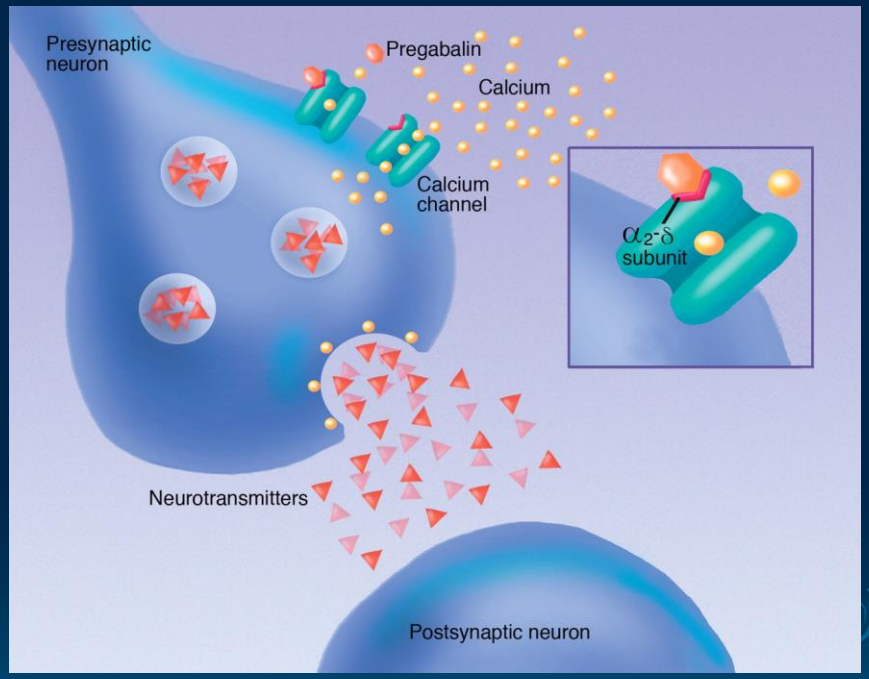
Lyrica®	
Class	Gabapentinoid
Dose Range	150 mg daily in 2-3 doses, Max: 600 mg daily Capsules, ER Tablets, Oral Solution
Seizure Types	Lennox-Gastaut Syndrome (adjunctive, off label)



Source: Lyrica (pregabalin) [prescribing information]. New York, NY: Pfizer Inc; May 2018.
https://upload.wikimedia.org/wikipedia/commons/thumb/d/db/Gabapentinoid-structures.png/300px-Gabapentinoid-structures.png

Pregabalin

Lyrica®	
MOA	Binds α-2-δ subunit of voltage-gated Ca^{2+} channels modulating Ca^{2+} influx at the nerve terminals. Inhibits excitatory neurotransmitter release including glutamate, norepinephrine, serotonin, dopamine, substance P, and calcitonin gene-related peptide



Source: Lyrica (pregabalin) [prescribing information]. New York, NY: Pfizer Inc; May 2018.
http://www.ajhp.org/content/ajhp/64/14/1475/F2.large.jpg

Pregabalin

Lyrica®	
Side Effects	Peripheral edema, weight gain, xerostomia, visual disturbances, suicidal ideation
Caution	Renally adjusted, multiple indications
CI	Hypersensitivity to pregabalin

Source: Lyrica (pregabalin) [prescribing information]. New York, NY: Pfizer Inc; May 2018.

Pregabalin

- Cost
  - $8.92/capsule
- Monitoring
  - None
- Pregnancy Category
  - Pregabalin crosses the placenta
  - Secreted in breast milk (RID ~7%)
  - Temporarily decreases sperm concentrations
- Renal Cutoff
  - CrCl = 60 mL/min

Source: Lyrica (pregabalin) [prescribing information]. New York, NY: Pfizer Inc; May 2018.

Pregabalin

- Place in Therapy
  - **Level A** – Treatment Resistant Focal Epilepsy
    - Adjunctive Therapy in Adults
    - Immediate release
  - **Level C** – New Onset Epilepsy with Focal Epilepsy or Unclassified Tonic-Clonic Seizures
    - Monotherapy in Adults
    - Recommendation against Lamotrigine is better

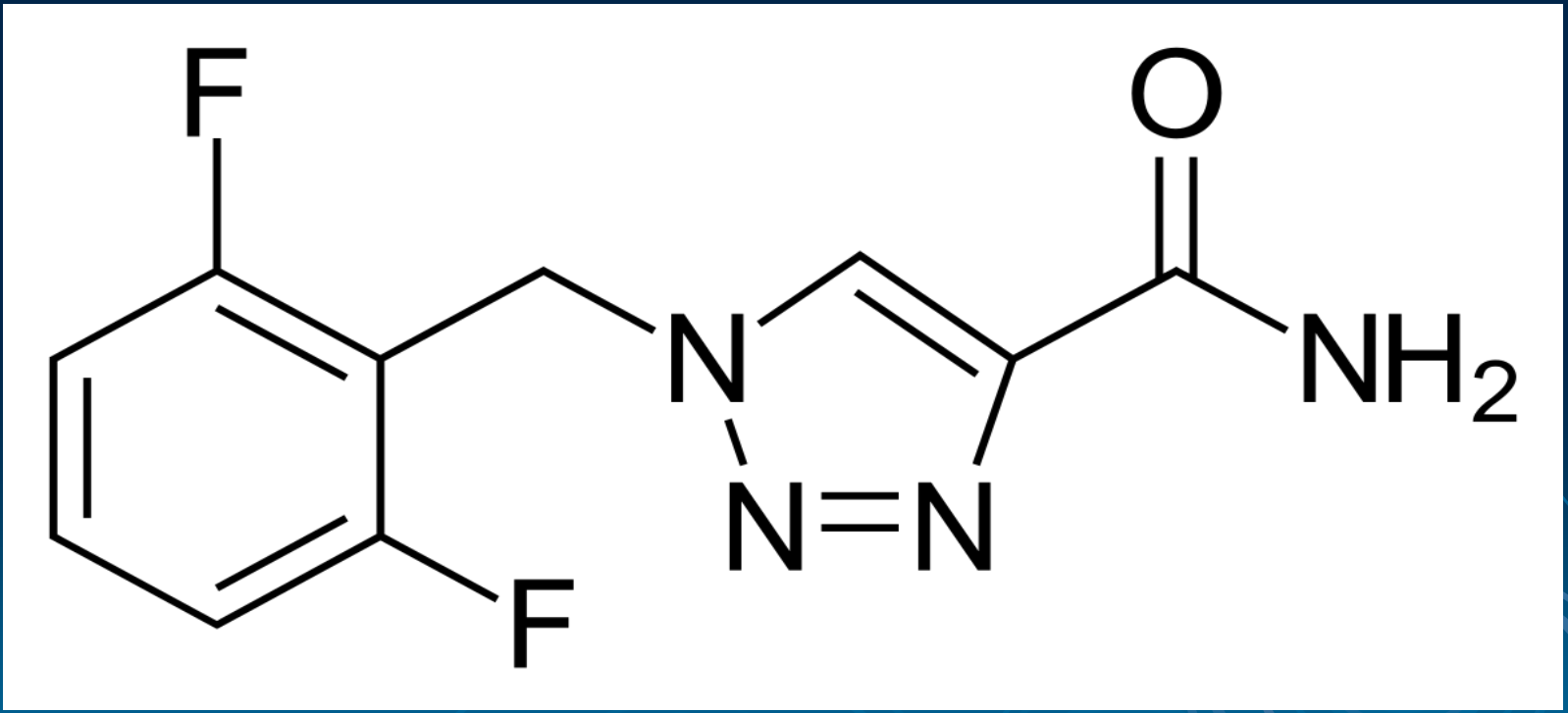
Rufinamide (ruh-fin-ah-mide)

Banzel®	
Class	Triazole Derivative
Dose Range	400 to 800 mg daily in 2-3 doses, Max: 3,200 mg daily Tablets, Suspension
Seizure Types	Lennox-Gastaut (adjunctive, FDA approved)

Source: Banzel (rufinamide) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; June 2015.
https://images.rxlist.com/images/multum/628560582_pb.jpg

Rufinamide

Banzel®	
MOA	Exact mechanism is unknown In vitro, prolongs inactive state of Na^+ Channels



Source: Banzel (rufinamide) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; June 2015.
https://upload.wikimedia.org/wikipedia/commons/thumb/e/e5/Rufinamide.svg/1200px-Rufinamide.svg.png

Rufinamide

Banzel®	
Side Effects	Shortened QT (46-65%), Multiorgan Sensitivity Reactions, Suicidal Ideation
Caution	Renally adjusted, if concomitant Valproate starting dose of Rufinamide should be <400 mg/day
CI	Patients with familial short QT syndrome, Hypersensitivity to Rufinamide

Source: Banzel (rufinamide) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; June 2015.

Rufinamide

- Cost
  - 200 mg tablet - $13.84
  - 400 mg tablet - $27.68
- Monitoring
  - None
- Pregnancy Category
  - C- Adverse effects in animal studies
  - Hormonal contraceptives less effective
  - Milk excretion unknown
- Hepatic Cutoff
  - Severe Impairment – Not recommended

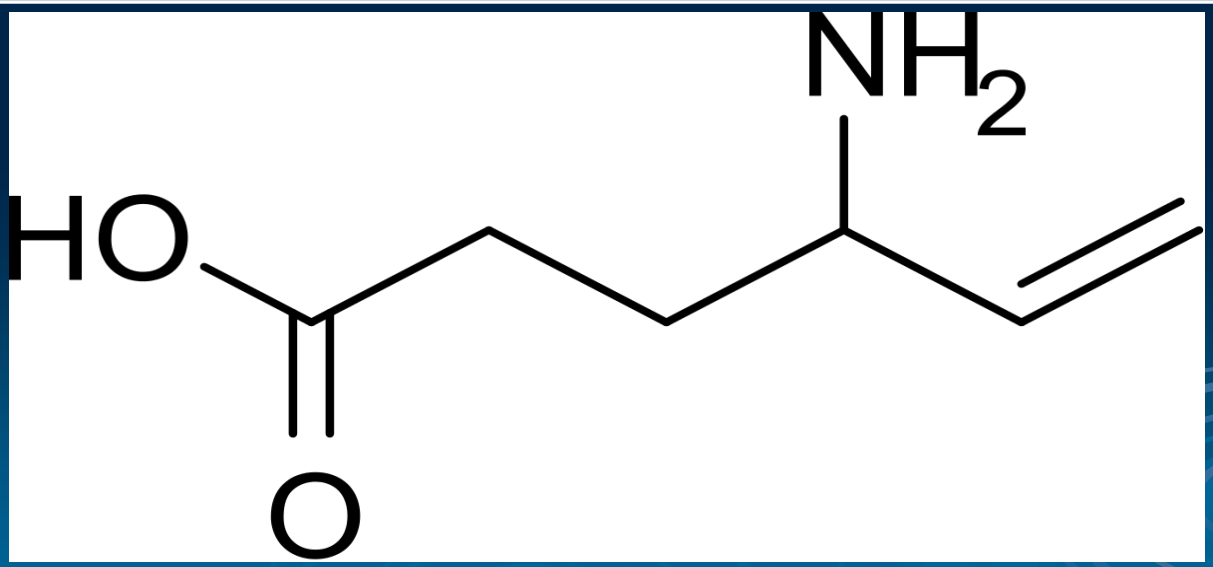
Source: Banzel (rufinamide) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; June 2015.

Rufinamide

- Place in Therapy
  - **Level A** – Treatment Resistant Focal Epilepsy
    - Adjunctive Therapy in Adults
    - Not first line
  - **Level A** - Lennox-Gastaut Syndrome
    - Adjunctive Therapy in Adults and Pediatrics
    - Effective as add-on therapy

Vigabatrin (vih-gab-ah-trin)

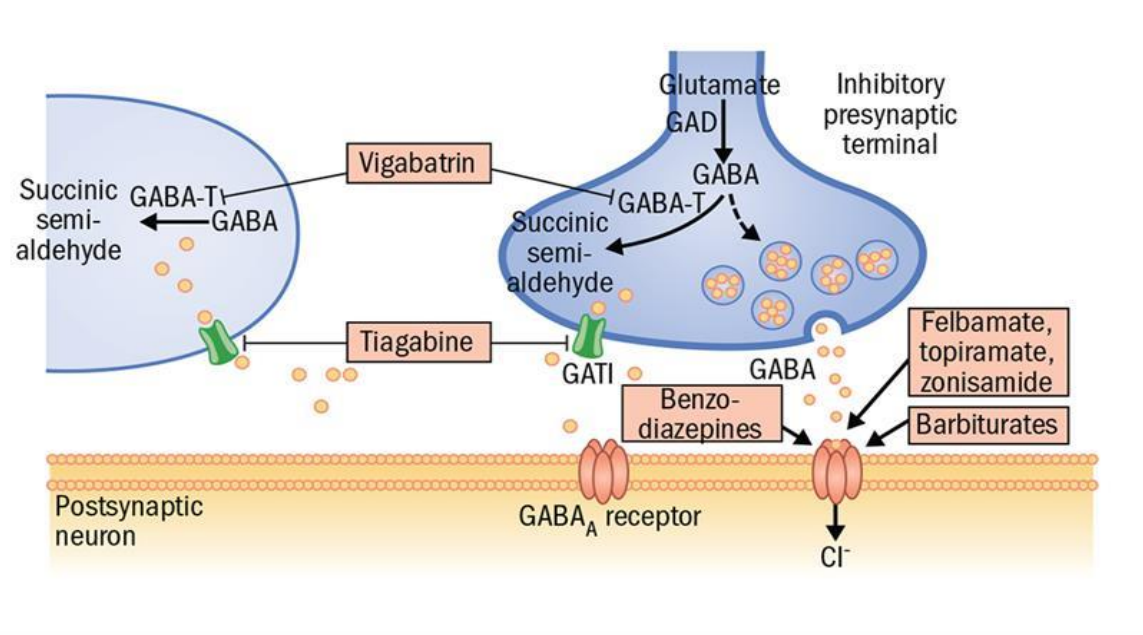
Sabril®	
Class	Structural analogue of GABA
Dose Range	500 mg BID, Recommended dose: 1.5 g BID Tablets, Packet
Seizure Types	Refractory complex partial seizures (FDA approved)



Source: Sabril (vigabatrin) [prescribing information]. Deerfield, IL: Lundbeck; February 2018.
https://upload.wikimedia.org/wikipedia/commons/thumb/0/04/Vigabatrin2DCSD.svg/1200px-Vigabatrin2DCSD.svg.png

Vigabatrin

Sabril®	
MOA	Irreversibly inhibits gamma-aminobutyric acid transaminase (GABA-T), increasing the levels of the inhibitory compound gamma amino butyric acid (GABA) within the brain. Duration of effect is dependent upon rate of patient GABA-T resynthesis.



Source: Sabril (vigabatrin) [prescribing information]. Deerfield, IL: Lundbeck; February 2018.
http://assets.markallengroup.com/article-images/image-library/147/Fig8blood.jpg

Vigabatrin

Sabril®	
Side Effects	Viral Infection (20% in infants), Irritability (16-23% in infants), Tremor (15%), Visual field loss (≥30%), Nystagmus, Blurred vision, Otitis media (10-44% infants), URTI (7%), Fever (4%)
Caution	Vision Loss (Black Box Warning), REMS
CI	Hypersensitivity to Vigabatrin

Source: Sabril (vigabatrin) [prescribing information]. Deerfield, IL: Lundbeck; February 2018.

Vigabatrin

- Cost
  - $126.64 – $159.55 per 500 mg
- Monitoring
  - Vision assessments (4 weeks, 3 months)
- Pregnancy Category
  - C – Adverse events in animal studies
  - Crosses placenta
  - Birth defects – Limb defects, male genital malformations, fetal anticonvulsant syndrome, renal and ear abnormalities
- Renal Cutoff
  - 80 mL/min

Source: Sabril (vigabatrin) [prescribing information]. Deerfield, IL: Lundbeck; February 2018.

Vigabatrin

- Place in therapy
  - **Level A** – Treatment Resistant Focal Epilepsy
    - Adjunctive Therapy in Adults
    - Not first line – Vision loss
  - **Level C** - New Onset Epilepsy with Focal Epilepsy or Unclassified Tonic-Clonic Seizures
    - Monotherapy in Adults
    - Not first line

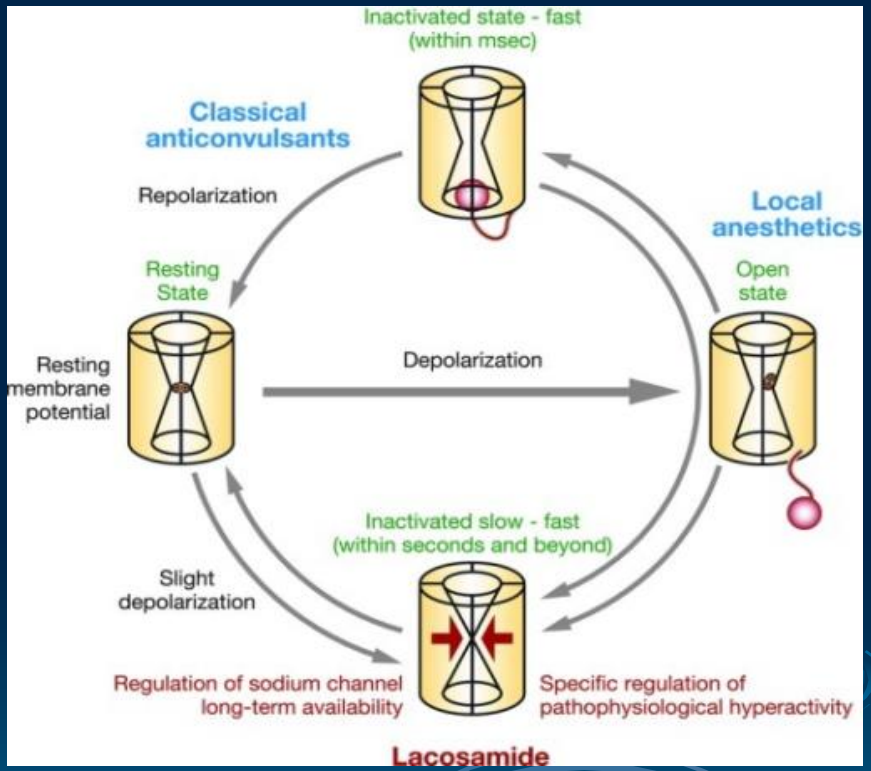
Lacosamide (la-KOE-sa-mide)

Vimpat®	
Class	Functionalized Amino Acid
Dose Range	Monotherapy: 100 mg BID, can increase by 50 mg BID OR 200 mg LD f/b 100 mg BID, can increase by 50 mg BID Adjunctive: 50 mg BID, can increase by 50 mg BID
Seizure Types	Partial onset seizure (monotherapy or adjunctive, FDA approved) Status epilepticus, refractory

Source: Vimpat (lacosamide) [prescribing information]. Smyrna, GA: UCB Inc; November 2018.

Lacosamide

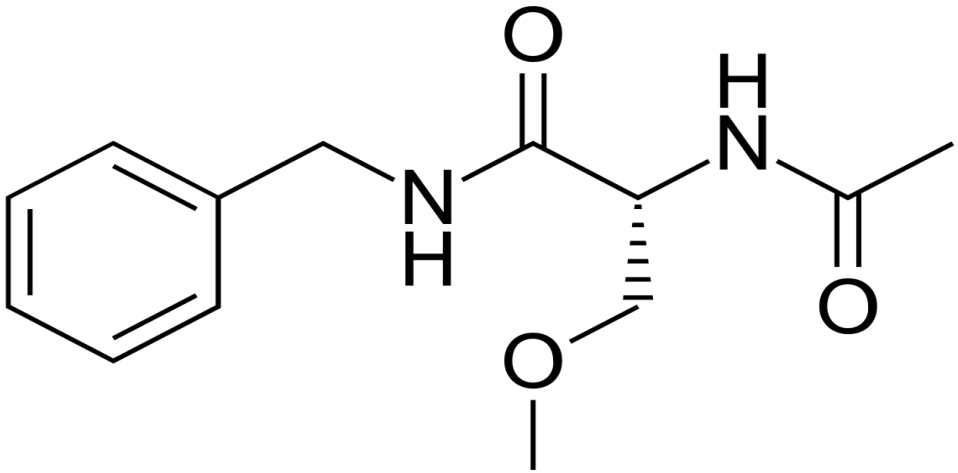
Vimpat®	
MOA	In vitro, stabilizes hyper excitable neuronal membranes and inhibits repetitive neuronal firing by enhancing the slow inactivation of sodium channels



Source: Vimpat (lacosamide) [prescribing information]. Smyrna, GA: UCB Inc; November 2018.
https://openi.nlm.nih.gov/imgs/512/329/3759704/PMC3759704_nyas1291-0056-f1.png

Lacosamide

Vimpat®	
Side Effects	Dizziness, Fatigue, Ataxia, Headache, N/V, Tremor, Diplopia, Blurred vision
Caution	PR interval prolongation, cardiac arrhythmia, AV block, V Tach, Multiorgan hypersensitivity, DRESS, Blurred vision, Diplopia, Suicidal ideation
CI	Hypersensitivity to Lacosamide



Source: Vimpat (lacosamide) [prescribing information]. Smyrna, GA: UCB Inc; November 2018.
https://upload.wikimedia.org/wikipedia/commons/thumb/d/d8/Lacosamide.svg/1200px-Lacosamide.svg.png

Lacosamide

- Cost
  - $10.33 – 50 mg, $16.16 – 100 mg, $17.11 – 150-200 mg
- Monitoring
  - Initial ECG in patients with cardiac issues
- Pregnancy Category
  - Adverse events in animal studies
- Renal Cutoff
  - 30 mL/min

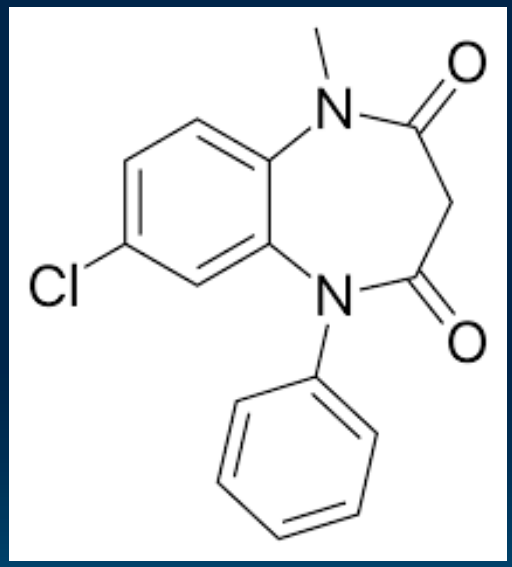
Source: Vimpat (lacosamide) [prescribing information]. Smyrna, GA: UCB Inc; November 2018.

Lacosamide

- Place in therapy
  - **Level B** – Treatment Resistant Focal Epilepsy
    - Adjunctive Therapy in Adults
    - Should be considered

Clobazam

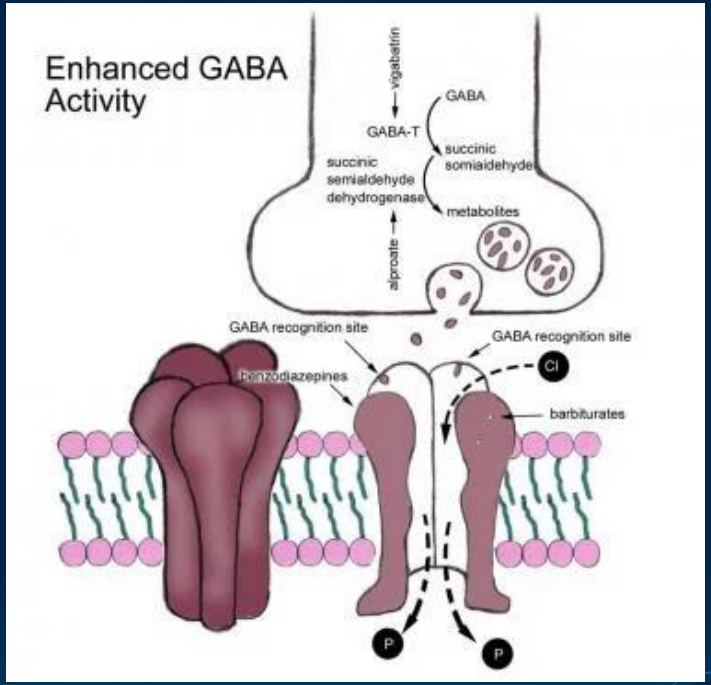
Onfi®	
Class	Benzodiazepine
Dose Range	Complex, see next slide Tablets, Solution
Seizure Types	Lennox-Gastaut (adjunctive, FDA Approved)



Source: Onfi (clobazam) [prescribing information]. Deerfield, IL: Lundbeck; June 2018.
https://upload.wikimedia.org/wikipedia/commons/thumb/f/f3/Clobazam_structure.svg/1200px-Clobazam_structure.svg.png

Clobazam

Onfi®	
MOA	Binds receptors the postsynaptic GABA neuron at several sites within the CNS. Enhances inhibitory effect of GABA on neuronal excitability by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization



Source: Onfi (clobazam) [prescribing information]. Deerfield, IL: Lundbeck; June 2018.
https://img.medscapestatic.com/pi/meds/ckb/94/7194tn.jpg

Clobazam

Onfi®	
Side Effects	Drooling (13-14%), Aggressive Behavior(8-14%), URTI (13-14%), Fever (10-17%), SJS, TEN
Caution	Anterograde Amnesia, SJS/TEN in first 8 weeks, Suicidal Ideation
CI	Hypersensitivity to Clobazam

Source: Onfi (clobazam) [prescribing information]. Deerfield, IL: Lundbeck; June 2018.

Clobazam Dosing

- >30 kg: Initial: 5 mg twice daily for ≥1 week, then increase to 10 mg twice daily for ≥1 week, then increase to 20 mg twice daily thereafter
- ≤30 kg: Initial: 5 mg once daily for ≥1 week, then increase to 5 mg twice daily for ≥1 week, then increase to 10 mg twice daily thereafter
- *CYP2C19 poor metabolizers:*
  - ≤30 kg: Initial: 5 mg once daily for ≥1 week, then increase to 5 mg twice daily; after ≥1 week may increase to 10 mg twice daily
  - >30 kg: Initial: 5 mg once daily for ≥1 week, then increase to 5 mg twice daily for ≥1 week, then increase to 10 mg twice daily; after ≥1 week may increase to 20 mg twice daily

Source: Onfi (clobazam) [prescribing information]. Deerfield, IL: Lundbeck; June 2018.

Clobazam Dosing

- Cost
  - Solution - $0.80 per 2.5 mg
  - Tablets - 10 mg - $2.29-21.97, 20 mg - $4.53-43.93
- Monitoring
  - Serious Skin Reactions
- Pregnancy Category
  - Crosses the placenta
  - Increased fetal malformations in 1st trimester
- Hepatic Cutoff
  - Adjusted in mild to moderate hepatic impairment

Source: Onfi (clobazam) [prescribing information]. Deerfield, IL: Lundbeck; June 2018.

Clobazam Dosing

- Place in therapy
  - **Level C** – Treatment Resistant Focal Epilepsy
    - Adjunctive Therapy in Adults
    - May be considered
  - **Level B** - Lennox-Gastaut Syndrome
    - Adjunctive Therapy in Adults and Pediatrics
    - Should be considered

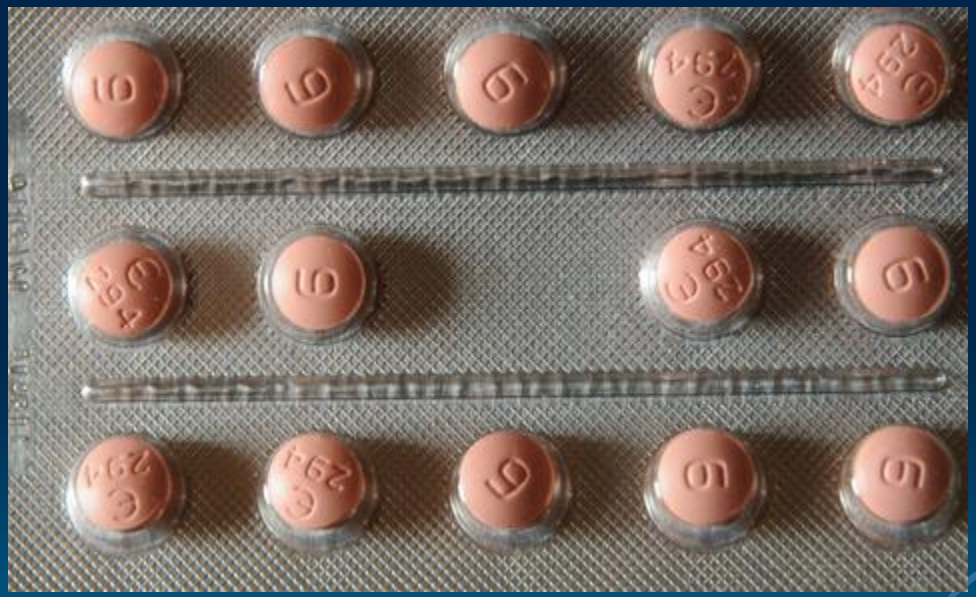
Perampanel

Fycompa®	
Class	AMPA Glutamate Receptor Antagonist
Dose Range	Patients not on enzyme inducing therapy:2 mg daily HS Increase by 2 mg daily. Up to 12 mg daily HS Patients on enzyme inducing therapy: 4 mg daily HS Increase by 2 mg daily. Up to 12 mg daily HS Tablets, Solution
Seizure Types	Partial Onset Seizure w/ or w/o secondarily generalized seizure (FDA approved) Primary generalized tonic-clonic seizures (adjunctive, FDA approved)

Source: Fycompa (perampanel) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; September 2018.

Perampanel

Fycompa®	
MOA	Exact mechanism unknown. It is a noncompetitive antagonist of AMPA glutamate receptor postsynaptically.



Source: Fycompa (perampanel) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; September 2018.

Source: https://qtxasset.com/styles/breakpoint_sm_default_480px_w/s3/2016-06/fycompa.JPG?jeJtzbE7kmvMC8yjAac.b4idRU.DMfAa&itok=0Ll1zZIe

Perampanel

Fycompa®	
Side Effects	Peripheral Edema (2%), Dizziness (16-≤47%), Hostility (≤12%-≤20%), Aggressive Behavior (2%-≤20%), delusion, disorientation, emotional lability, homicidal ideation, paranoia, psychiatric disturbance (worsening)
Caution	Black Box Warning: Serious Psychiatric and Behavioral Reactions
CI	Hypersensitivity to Perampanel

Source: Fycompa (perampanel) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; September 2018.

Perampanel

- Cost
  - Tablet - 2 mg - $18.08 – 4, 6, 8, 10, 12 mg - $35.88
- Monitoring
  - Suicidal thoughts, depression, behavioral changes during therapy and for 1 month after D/C
- Pregnancy Category
  - Adverse events in animal studies
  - Contraceptives containing levonorgestrel may be less effective
- Renal Cutoff
  - <50 mL/min

Source: Fycompa (perampanel) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; September 2018.

Perampanel

- Place in therapy
  - **Level A** – Treatment Resistant Focal Epilepsy
    - Adjunctive Therapy in Adults
    - Established as effective

Eslicarbazepine (Es-li-kar-baz-e-peen)

Aptiom®	
Dose Range	Initial: 400 or 800 mg PO QD. Titrate weekly in 400-600 mg increments. Maintenance: 800-1,600 mg QD. Monotherapy: Consider 800 mg QD 1,200 mg QD if not tolerating. Adjunctive Therapy: Consider 1,200 mg QD - 1,600 mg QD if inadequate seizure response.
Seizure Types	Partial Onset Seizure (FDA approved)

Source: Aptiom (eslicarbazepine) [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals; October 2017.

Eslicarbazepine

Aptiom®	
MOA	A precise mechanism has not been defined, but is thought to involve inhibition of voltage-gated sodium channels.

Source: Aptiom (eslicarbazepine) [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals; October 2017.
https://img.medscapestatic.com/pi/features/drugdirectory/octupdate/SPI02060.jpg

Eslicarbazepine

Aptiom®	
Side Effects	Dizziness, Drowsiness, Nausea, Diplopia (9-11%)
Caution	Hazardous agent (NIOSH 2016 group 3), use gloves when handling, unpacking, or placing in storage. Increased risk of visual changes and coordination abnormalities during titration period in patients >60 Risk for SJS, multiorgan hypersensitivity reactions, DRESS Dose dependent decreases in T3 and T4 values
CI	Hypersensitivity to Eslicarbazepine, Oxacarbazepine

Source: Aptiom (eslicarbazepine) [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals; October 2017.

Eslicarbazepine

- Cost
  - Tablet – 200-800 mg - $36.71
- Monitoring
  - Sodium during maintenance if patient receiving other sodium depleting drugs
- Pregnancy Category
  - Adverse events in animal studies
  - May decrease plasma levels of hormonal contraceptives
  - Excreted in breast milk
- Renal Cutoff
  - <50 mL/min

Source: Aptiom (eslicarbazepine) [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals; October 2017.

Eslicarbazepine

MEDICATION GUIDE
APTIOM (ap tee' om)
(eslicarbazepine acetate)
tablets

What is the most important information I should know about APTIOM?

- **Do not stop taking APTIOM without first talking to your healthcare provider.**
  - Stopping APTIOM suddenly can cause serious problems. Stopping a seizure medicine suddenly in a patient who has epilepsy may cause seizures that will not stop (status epilepticus).

1. Like other antiepileptic drugs, APTIOM may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- new or worse depression
- feeling agitated or restless
- trouble sleeping (insomnia)
- acting aggressive, being angry, or violent
- an extreme increase in activity and talking (mania)
- attempt to commit suicide
- new or worse anxiety
- panic attacks
- new or worse irritability
- acting on dangerous impulses
- other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Suicidal thoughts or actions may be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

2. APTIOM may cause allergic reactions or serious problems which may affect organs and other parts of your body like the liver or blood cells. You may or may not have a rash with these types of reactions.

Call your healthcare provider right away if you have any of the following:

- swelling of your face, eyes, lips, or tongue
- a skin rash
- trouble swallowing or breathing
- hives

Eslicarbazepine

- Place in therapy
  - **Level C** – Treatment Resistant Focal Epilepsy
    - Monotherapy in Adults
    - May be considered
  - **Level B** – Treatment Resistant Focal Epilepsy
    - Adjunctive Therapy in Adults
    - Should be considered

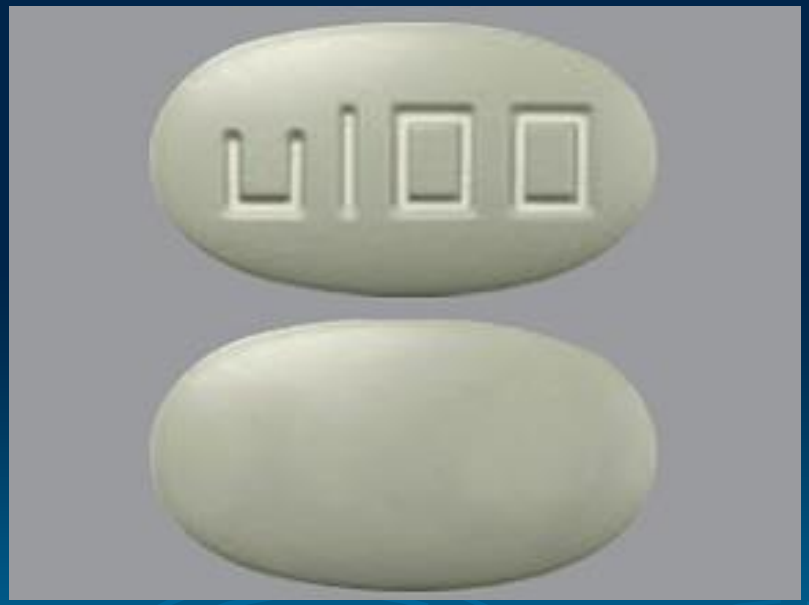
Brivaracetam (Briv-a-ra-se-tam)

Briviact®	
Class	Racetam Derivative/Analogue of Leviteracetam
Dose Range	Monotherapy and Adjunctive: 50 mg BID initially, may decrease to 25 mg BID or increase to 100 mg BID based on response and tolerability Maximum dose: 200 mg total daily If used with Rifampin, double the dose. Major substrate of 2C19
Seizure Types	Partial onset seizures (FDA approved)

Source: Briviact (brivaracetam) [prescribing information]. Smyrna, GA: UCB; May 2018.

Brivaracetam

Briviact®	
MOA	Unknown. High selectivity for synaptic vesicle protein 2A (same protein as leviteracetam) with a 20x more affinity



Source: Briviact (brivaracetam) [prescribing information]. Smyrna, GA: UCB; May 2018.
https://img.medscapestatic.com/pi/features/drugdirectory/octupdate/UCB07700.jpg

Brivaracetam

Briviact®	
Side Effects	Drowsiness, Fatigue, Hypersomnia, Malaise, Abnormal Gait, Ataxia, Equilibrium disturbance, Vertigo, Psychotic and Nonpsychotic Psychiatric Disturbances (13%), Asthenia, Nystagmus
Caution	Must be tapered off, Hematologic abnormalities, Psychiatric disturbances
CI	Hypersensitivity to Brivaracetam

Source: Briviact (brivaracetam) [prescribing information]. Smyrna, GA: UCB; May 2018.

Brivaracetam

- Cost
  - IV – 50 mg/mL – $11.01
  - Solution – 10 mg/mL - $4.28
  - Tablet – 10, 25, 50, 75, 100 mg - $21.40
- Monitoring
  - CBC, liver and renal function, depression, and suicidality (baseline and if clinically indicated)
- Pregnancy Category
  - Adverse events in animal studies
- Hepatic Cutoff
  - Mild to severe – Start at 25 mg, Maximum dose of 75 mg

Source: Briviact (brivaracetam) [prescribing information]. Smyrna, GA: UCB; May 2018.

Brivaracetam

- Place in therapy
  - ?

Cannibidiol Solution

FDA News Release

FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy

For Immediate Release June 25, 2018

Release

Español

The U.S. Food and Drug Administration today approved Epidiolex (cannabidiol) [CBD] oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older. This is the first FDA-approved drug that contains a purified drug substance derived from marijuana. It is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome.

CBD is a chemical component of the Cannabis sativa plant, more commonly known as marijuana. However, CBD does not cause intoxication or euphoria (the "high") that comes from tetrahydrocannabinol (THC).

It is THC (and not CBD) that is the primary psychoactive component of marijuana.

Cannabidiol Solution

Epidiolex®	
Class	Phytocannabinoid
Dose Range	2.5 mg/kg BID, after 1 week may increase to 5 mg/kg BID May increase in weekly increments of 2.5 mg/kg BID Maximum Dose: 10 mg/kg BID Oral Solution
Seizure Types	Lennox-Gastaut in patients 2 years or older (FDA Approved) Dravet Syndrome in patients 2 years or older(FDA Approved)
MOA	Unknown. It does not appear to involve its effects on cannabinoid receptors.
Side Effects	Somnolence, Decreased Appetite, Diarrhea, Transaminase Elevations, Fatigue, Malaise, Asthenia, Rash, Insomnia, Sleep Disorder, Poor Quality of Sleep, Infections
Caution	Taper Off, Hepatically adjusted, 20 mg/kg/day resulted in greater reduction in seizure rates but had increases in adverse drug reactions
CI	Hypersensitivity to cannabidiol

Cannabidiol Solution

- Cost
  - Solution 100 mg/mL - $14.82
    - (75 kg $55.56 - $222.30 per day)
- Monitoring
  - ALT, AST, bilirubin (0, 1, 3, and 6 months)
  - Periodic monitoring as clinically indicated (dose change or starting hepatotoxic drug or clinical signs of hepatic dysfunction)
- Pregnancy Category
  - Adverse events in animal studies
  - Cannabidiol can be detected in the umbilical cord and meconium following maternal use of inhaled, non-medicinal cannabis during pregnancy

Source: Epidiolex (cannabidiol) [prescribing information]. Carlsbad, CA: Greenwich Biosciences, Inc; September 2018.

Cannabidiol Solution

- Hepatic Cutoff
  - Moderate – Start at 1.25 mg/kg BID with slow increases
  - Severe – Start at 0.5 mg/kg BID with slow increases
- Hepatotoxicity during treatment:
  - AST and/or ALT >3 times ULN and total bilirubin >2 times ULN: Discontinue treatment.
  - Sustained AST and/or ALT >5 times ULN: Discontinue treatment.

Source: Epidiolex (cannabidiol) [prescribing information]. Carlsbad, CA: Greenwich Biosciences, Inc; September 2018.

Cannabidiol Solution

- Place in therapy
  - ?

Cannabidiol Legality

Drug Enforcement Administration

DEA Headquarters

@DEAHQ

September 27, 2018 **FOR IMMEDIATE RELEASE**

Contact: National Media Affairs Office

Phone Number: (202) 307-1000

FDA-approved drug Epidiolex placed in schedule V of Controlled Substance Act

WASHINGTON - The Department of Justice and Drug Enforcement Administration today announced that Epidiolex, the newly approved medication by the Food & Drug Administration, is being placed in schedule V of the Controlled Substances Act, the least restrictive schedule of the CSA.

In June 2018, the FDA announced it approved Epidiolex for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older.

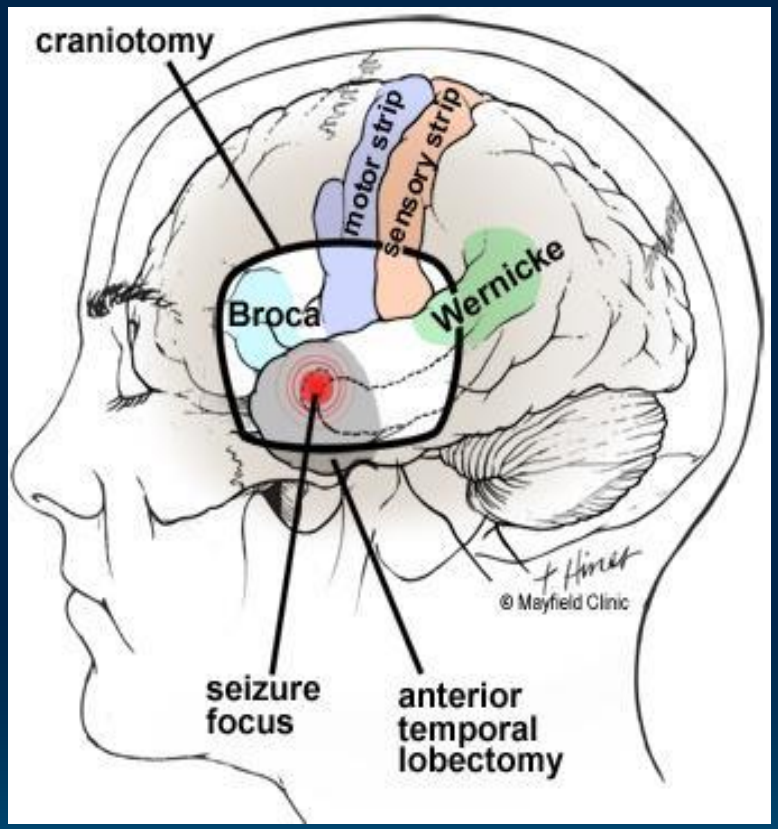
Epidiolex contains cannabidiol (CBD), a chemical constituent of the cannabis plant (commonly referred to as marijuana). The CBD in Epidiolex is extracted from the cannabis plant and is the first FDA-approved drug to contain a purified extract from the plant.

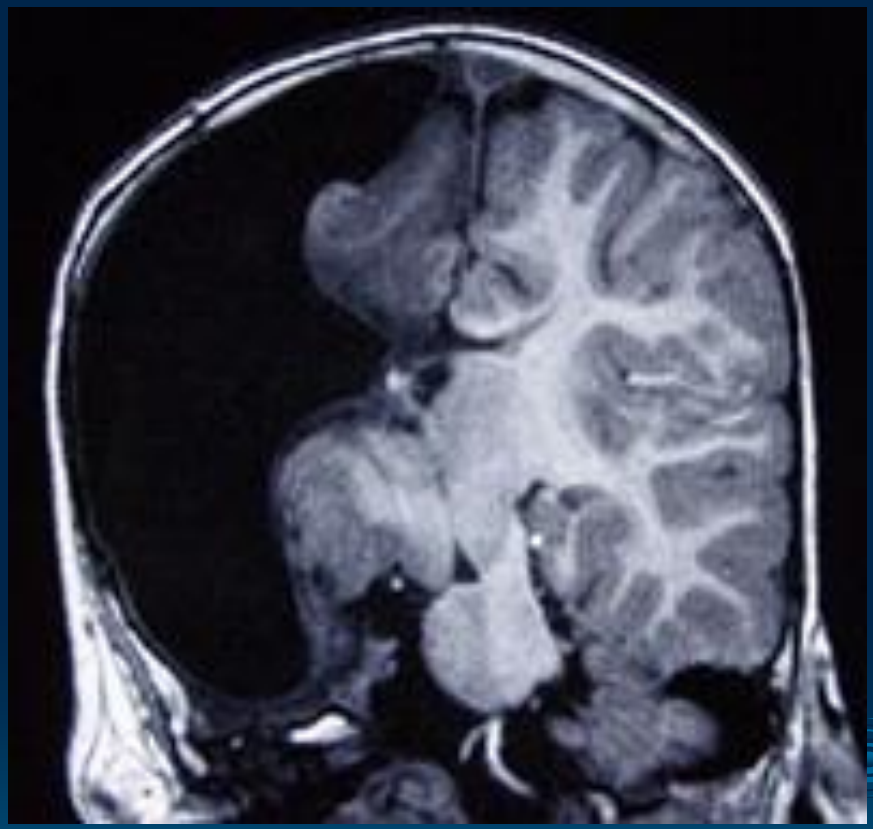
Non Pharmacological Therapy

Epilepsy Surgery

- Focal Resection
  - Temporal Lobe Resection
  - Frontal, Parietal, Occiptal Lobe Resection
- Lesionectomy
- Laser Interstitial Thermal Therapy
- Anatomical or Functional Hemispherectomy/ Hemispherotomy
- Corpus Callostomy
- Stereotactic Radiosurgery

Epilepsy Surgery

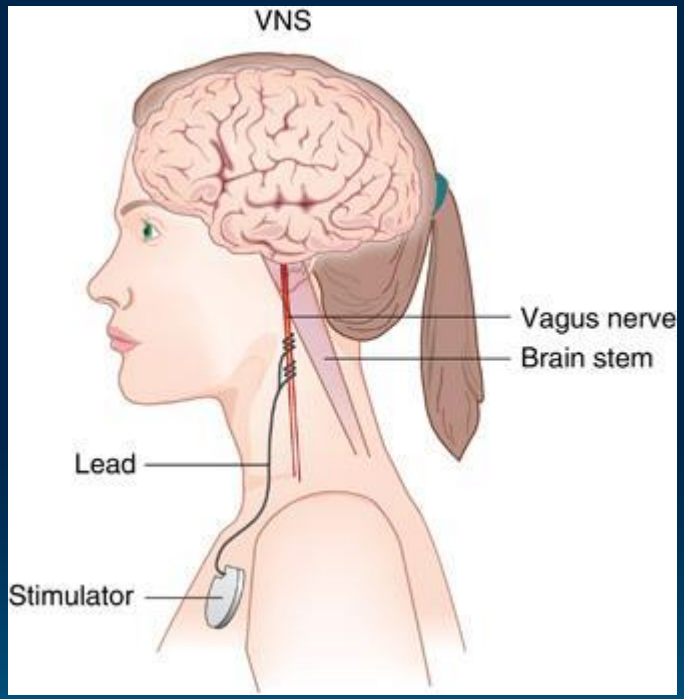




Source: https://mayfieldclinic.com/Images/pe-epilepsy-surgery-fig3.jpg
https://my.clevelandclinic.org/-/scassets/ad37970506424f408a6aa3c46f5596cc.ashx

Neurostimulation Devices

- Vagus Nerve Stimulation (VNS)



Source: https://neuromodec.com/wp-content/uploads/2016/08/VNS.jpg

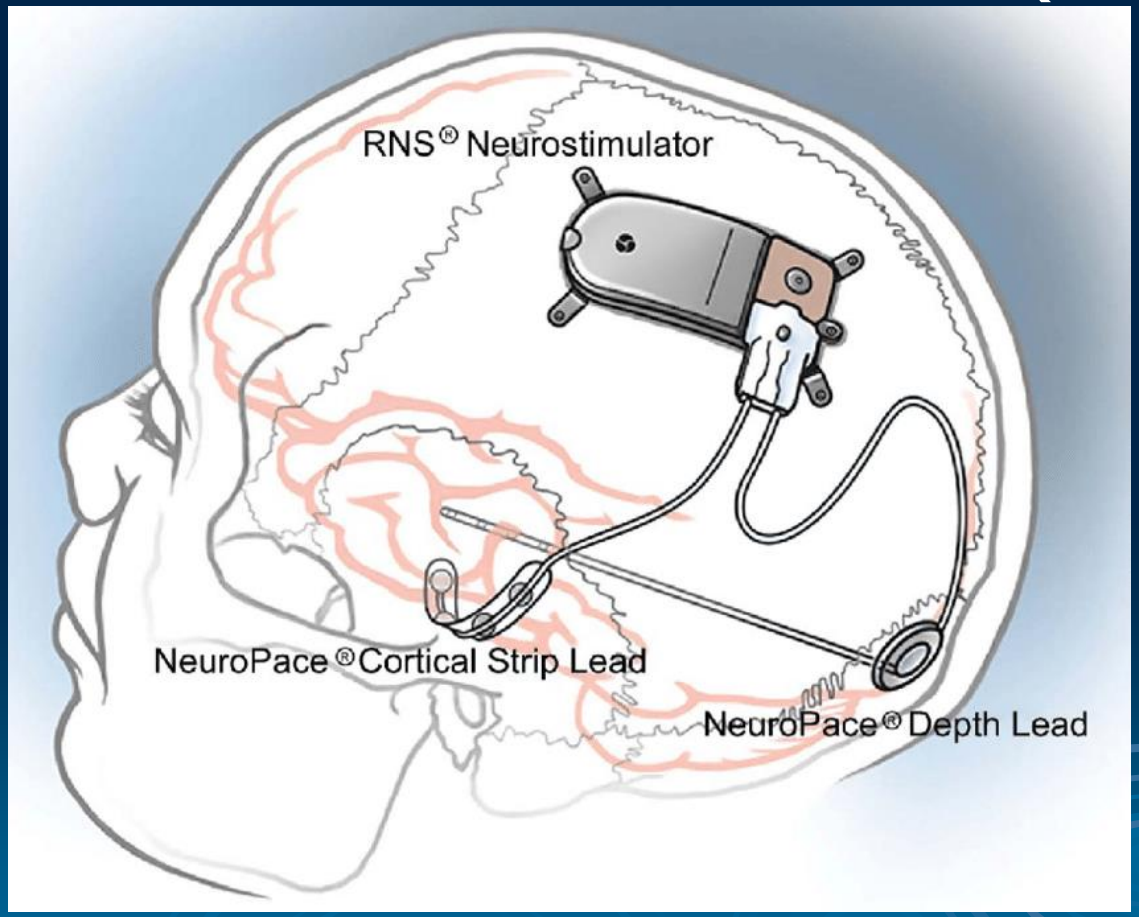
https://www.aans.org/-/media/Images/AANS/Neurosurgical-Conditions-and-Treatments/Lead_Vagus_Nerve_Stimulation.ashx?la=en&hash=FDCC6C03258B04D3BFE1E18B2F853D18AE6959E2

https://www.sciencesource.com/Doc/TR1_WATERMARKED/f/6/7/c/SS2758135.jpg?d63644360461

http://eu.cyberonics.com/static/images/27.jpg

Neurostimulation Devices

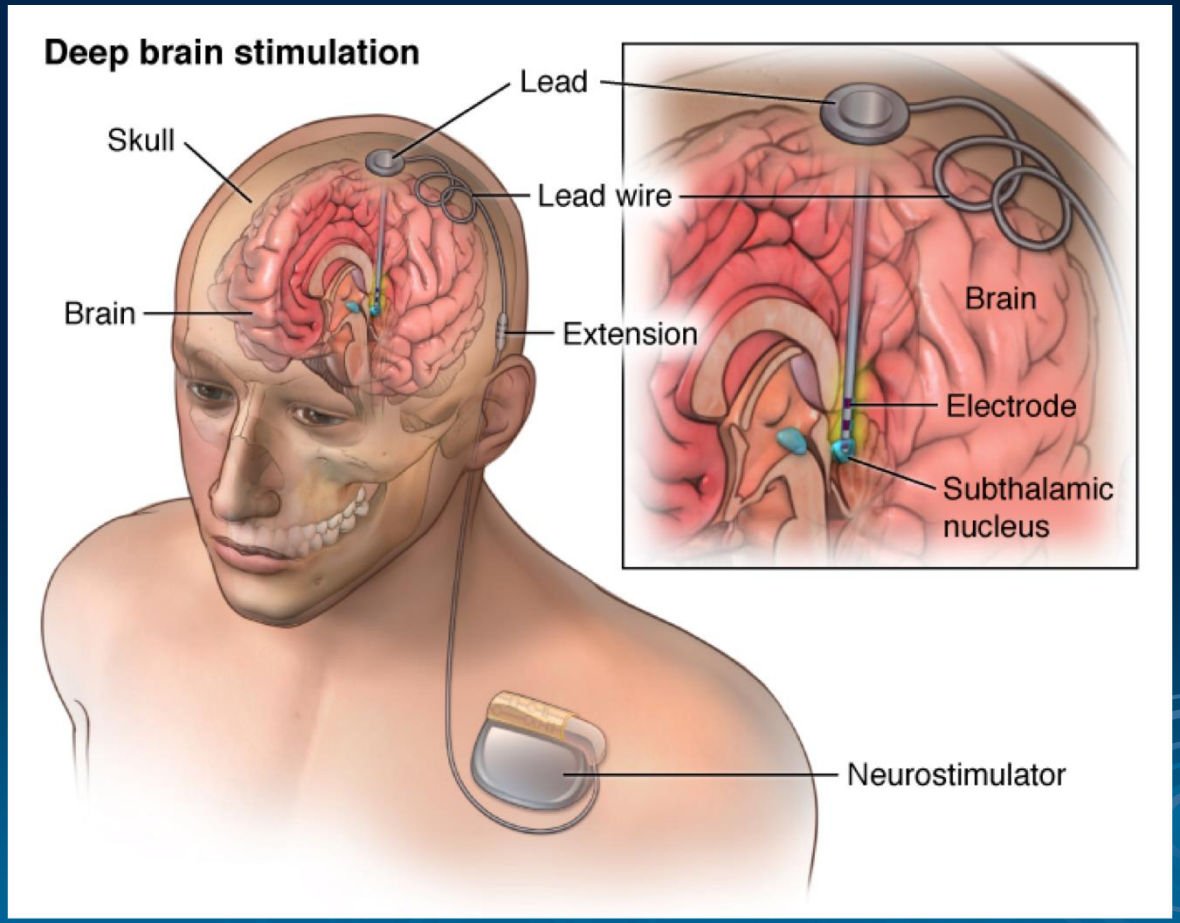
- Responsive Neurostimulation (RNS)



Source: https://www.pnas.org/content/pnas/112/49/15012/F2.large.jpg

Neurostimulation Devices

- Deep Brain Stimulation (DBS)



Source: http://www.parkinson.fo/myndir/myndin-162_r_960_620.jpg

Conclusion

- Since 2000, many new AEDs have been brought to market
  - Each has a place in managing epilepsy
- Epidiolex is the first FDA approved CBD derivative for treatment of Epilepsy
  - It is the only CBD derivative to be placed into Schedule V
- For treatment resistant epilepsy, we have newer medications as well as surgical and implantable means of managing the condition

Test Your Knowledge

1. True or False: Epidiolex (cannabidiol/CBD) is the first purified drug substance derived from marijuana to be FDA approved in the U.S.
2. True or False: Epidiolex (cannabidiol/CBD) has been placed into Schedule I by the DEA.
3. True or False: After the first seizure episode, a patient should be initiated on antiseizure therapy.