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Contemporary Epilepsy Management: Integrating the Latest Evidence Into Patient Care

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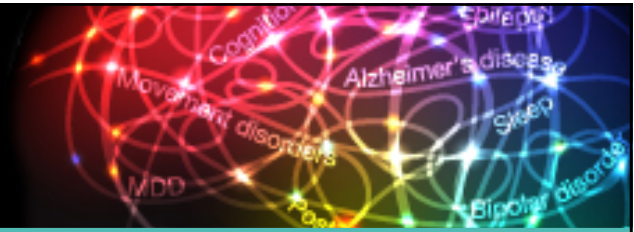
Mayo Clinic Arizona

Phoenix, AZ



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Disclosures



- ***Research/Grants:*** NeuroPace, Inc.
- ***Consultant:*** NeuroPace, Inc.; UCB, Inc.

Learning Objective 1

Implement the 2017 ILAE classification of seizure types into the diagnosis of patients with epilepsy.

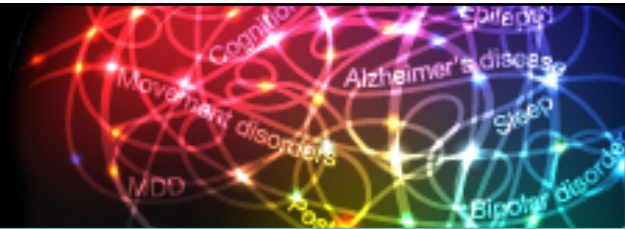


Learning Objective 2

Select the most appropriate type of antiepileptic agent based on patient factors and seizure type.

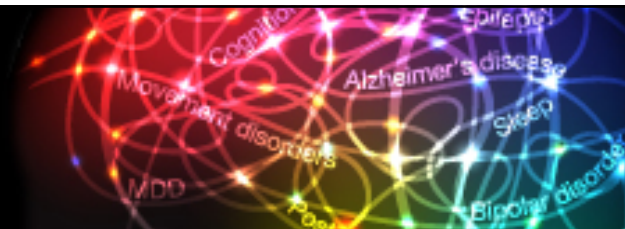


Classification



- Why do we keep changing the classification of seizures and epilepsy?
 - Needs to follow the logic of how health professionals communicate about seizures
 - Needs to keep up with our rapidly changing understanding of seizures and epilepsy as imaging and genetics continue to upend what we know about the condition.

Definitions



- Seizures:
 - "A transient symptom of excessive or synchronous neuronal activity in the brain" (ILAE)
 - A symptom NOT a diagnosis
- Epilepsy
 - 2 or more unprovoked seizures (old definition)
 - 60% chance of a seizure within the next 2 years (new definition)
 - Propensity for seizures to occur

ILAE = International League Against.
Fisher RS, et al. *Epilepsia*. 2017;58(4):522-530.

ILAE 2017 Classification of Seizure Types Expanded Version

Focal Onset

Aware

Impaired Awareness

Motor Onset
Automatisms
Atonic¹
Clonic
Epileptic spasms¹
Hyperkinetic
Myoclonic
Tonic
Non-Motor Onset
Autonomic
Behavior arrest
Cognitive
Emotional
Sensory

To Bilateral Tonic-Clonic

Generalized Onset

Motor
Tonic-clonic
Clonic
Tonic
Myoclonic
Myoclonic-tonic-clonic
Myoclonic-atic
Atonic
Epileptic spasms
Non-Motor (Absence)
Typical
Atypical
Myoclonic
Eyelid myoclonia

Unknown Onset

Motor
Tonic-clonic
Epileptic spasms
Non-motor
Behavior arrest

Unclassified²

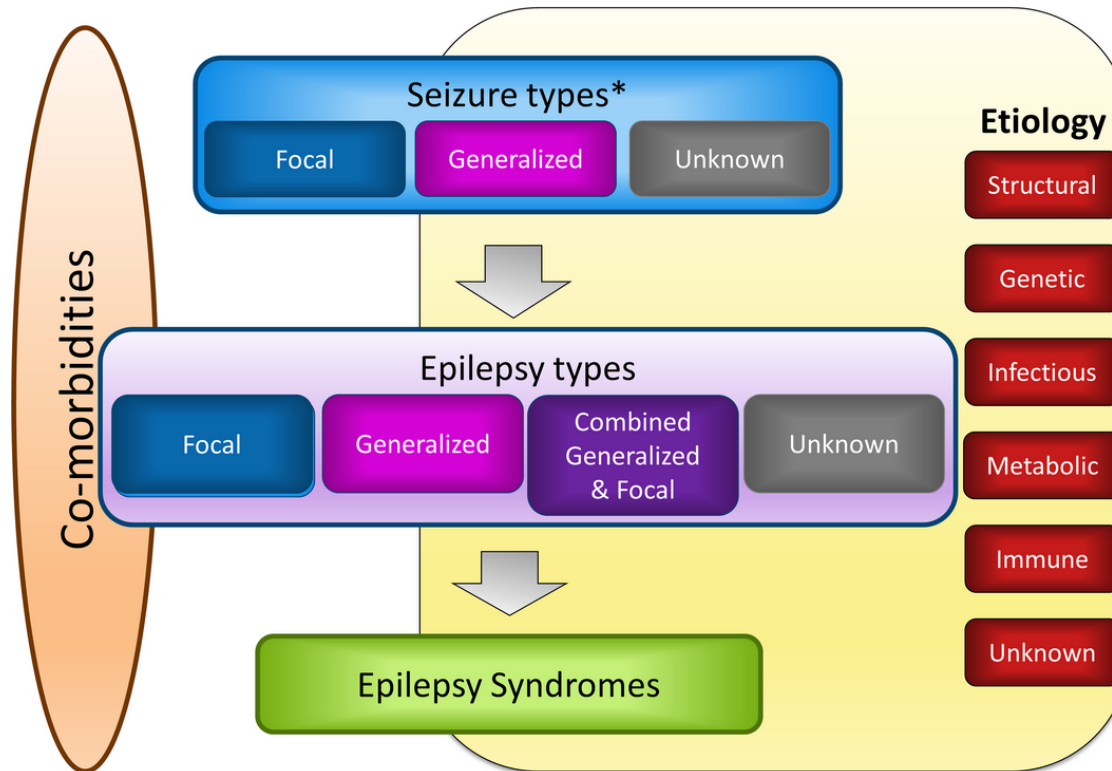
Most important are in teal

¹Degree of awareness usually not specified

²Due to inadequate information or inability to place in other categories

Fisher RS, et al. *Epilepsia*.2017;58(4):522-530.

ILAE Classification of the Epilepsies: Position Paper of the ILAE Commission for Classification and Terminology

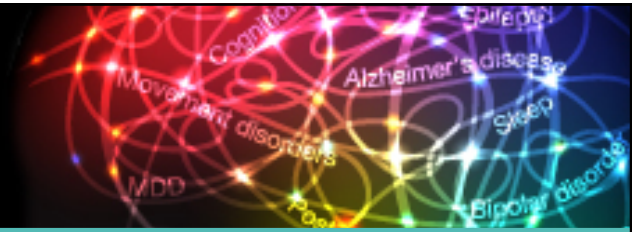


Scheffer IE, et al. *Epilepsia*. 2017;158(4):512-521.

Quick Case

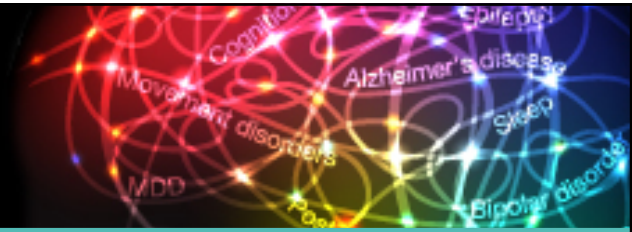


Quick Case



- 28-year-old female
 - Presents in clinic for evaluation after a second convulsion occurring 2 weeks ago
 - 1st event was 18 months prior
 - No provoking factors
 - Currently feels normal
- Upon, detailed history
 - ~1x/mo events of extreme déjà vu, followed by nausea and mild disorientation for 2 years

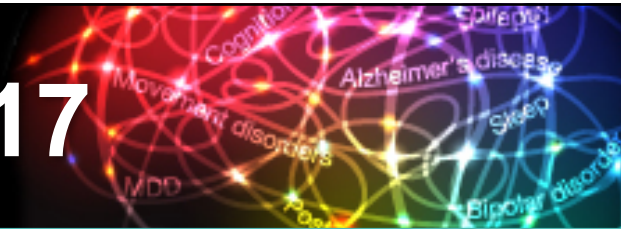
Case Continued



- Past medical history unremarkable
 - Records from ER were unremarkable
- MRI is normal
- EEG shows infrequent right temporal spike and wave discharges during drowsiness
- Patient was married 3 years ago and would like to start a family “soon”

ER = emergency room, MRI = magnetic resonance imaging, EEG = electroencephalogram.

Antiepileptic Drugs: US 2017



First Generation

- Carbamazepine
- Ethosuximide
- Phenytoin
- Phenobarbital
- Primidone
- Valproate

Second Generation

- Felbamate†
- Gabapentin
- Lamotrigine*
- Levetiracetam
- Oxcarbazepine*
- Tiagabine
- Topiramate*
- Zonisamide

Third Generation

- Brivaracetam
- Clobazam
- Eslicarbazepine
- Ezogabine†
- Lacosamide*
- Perampanel
- Pregabalin
- Rufinamide
- Vigabatrin†

*Approved for monotherapy.

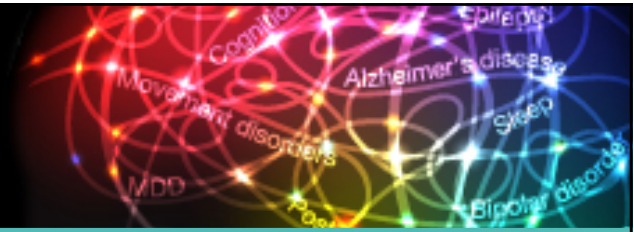
†Use limited due to safety concerns.

Which Treatment to Choose?



- 
- Lacosamide
 - Oxcarbazepine
 - Topiramate
 - Valproate
 - Vagus nerve stimulator
 - Rufinamide
 - Lamotrigine
 - Ketogenic diet
 - Phenytoin
 - Gabapentin
 - Tiagabine
 - Primidone
 - Zonisamide
 - Clonazepam
 - Felbamate
 - Ethosuximide
 - Phenobarbital
 - Carbamazepine
 - Pregabalin
 - Levetiracetam
 - Epilepsy surgery

How to Choose an AED?

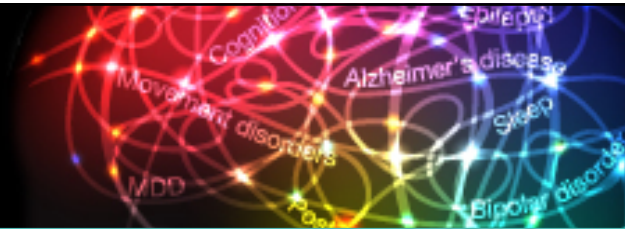


- New medications*
 - New-Old medications
 - New-New medications
- How to choose a medication*

AEDs = antiepileptic drugs

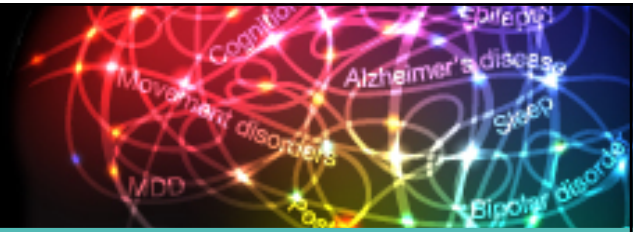
*Off label indications may be discussed.

New-Old Medications



- Clobazam
- Eslicarbazepine
- New extended release
 - Lamotrigine
 - Levetiracetam
 - Oxcarbazepine
 - Topiramate
 - Gabapentin

New-New Medications



- Brivaracetam
- Ezogabine*
- Lacosamide
- Perampanel

*Will be withdrawn from the market January 2018.

Brivaracetam – Son or Daughter of Levetiracetam The Latest Third Generation AED

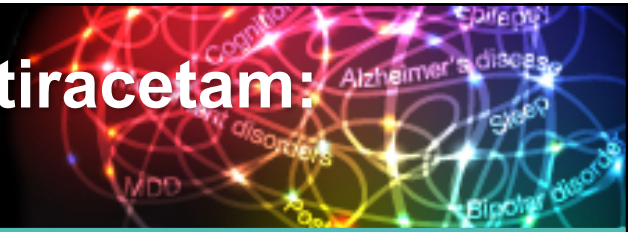
- Like LEV, BRV binds to SV2A receptor (15-30X greater affinity)
- ~100% bioavailability; $t_{1/2}$ 8 hrs
- < 20% protein bound
- No significant drug-drug interactions at doses \leq 200 mg/day; slight increase in phenytoin and carbamazepine epoxide metabolite.
- Can be rapidly introduced at therapeutic dose

LEV = levetiracetam, BRV = brivaracetam.

Klitgard H, et al. *Epilepsia*. 2016; 57:538-548; FDA.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205836Orig1s000,205837Orig1s000,205838Orig1s000lbl.pdf

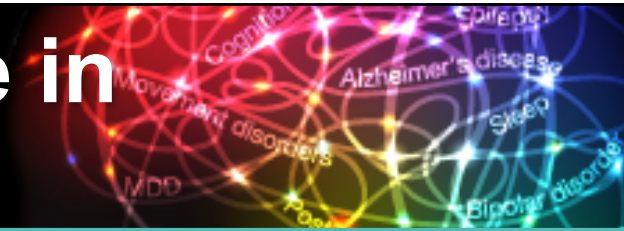
Brivaracetam – Son or Daughter of Levetiracetam: The Latest Third Generation AED



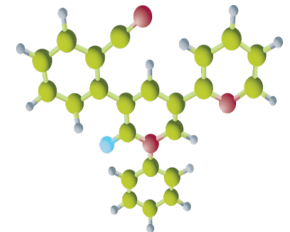
- Previous trials have shown efficacy at 50 mg/day and 150 mg/day doses but no dose response relationship.
- In another phase III trial 100 mg/day but not 50 mg/day was superior to placebo
- Maximum dose is ≤ 200 mg/day
- Excellent tolerability and lack of dose relationship and side effects

FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205836Orig1s000,205837Orig1s000,205838Orig1s000lbl.pdf;
Ben-Menachem E, et al. *Neurology*. 2016;87(3):314-323.

Perampanel: Rationale for Use in Treatment-Resistant Epilepsy



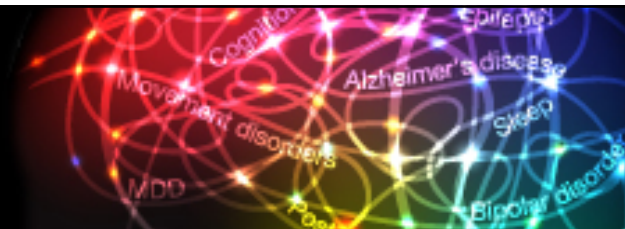
- AMPA receptors
 - Principal glutamate receptors that mediate fast excitatory neurotransmission¹
 - AMPA receptor antagonism can inhibit initiation and spread of seizure activity¹
- Perampanel
 - Selective, noncompetitive AMPA receptor antagonist^{2,3}
 - Reduces activation of AMPA receptors by glutamate, reducing the excitability of neurons expressing these receptors⁴
- Indicated for²:
 - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥12 years of age
 - Adjunctive therapy in the treatment of PGTC seizures in patients ≥12 years old



AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; PGTC = primary generalized tonic-clonic.

1. Hanada T, et al. *Epilepsia*. 2011;52:1331-1340; 2. FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202834lbl.pdf; 3. Rogawski MA, et al. *Acta Neurol Scand*. 2013;127(suppl 197):19-24; 4. Badawy RAB, et al. *Brain*. 2013;136(4):1177-1191.

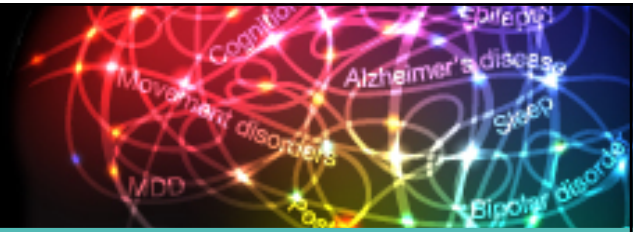
Broad Spectrum AEDs



- First generation
 - Valproate
- Second/Third generation
 - Clobazam*
 - Lamotrigine
 - Levetiracetam
 - Perampanel
 - Topiramate
 - Zonisamide*
 - Brivaracetam*

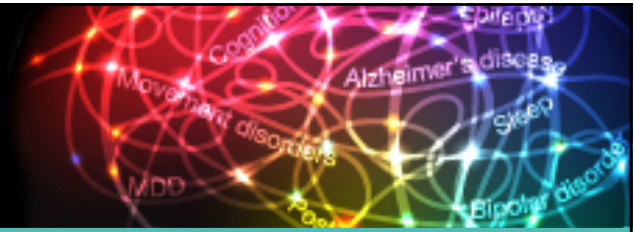
*Zonisamide and clobazam are not indicated for primary generalized seizures.

Side Effects – Mood



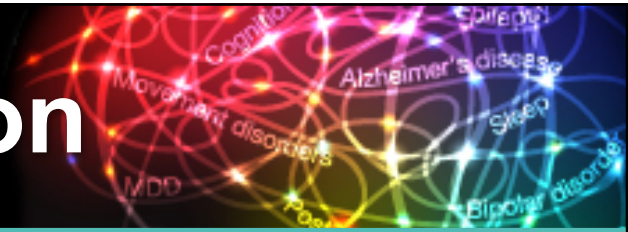
	Topiramate	
Valproate	Zonisamide	Levetiracetam
Lamotrigine	Oxcarbazepine	Lacosamide
		Perampanel
Carbamazepine	Phenytoin	
		Clobazam

Speed of Introduction



- IV Medications
 - Phenytoin
 - Fosphenytoin
 - Phenobarbital
 - Valproic acid
 - Levetiracetam
 - Lacosamide
 - Brivaracetam

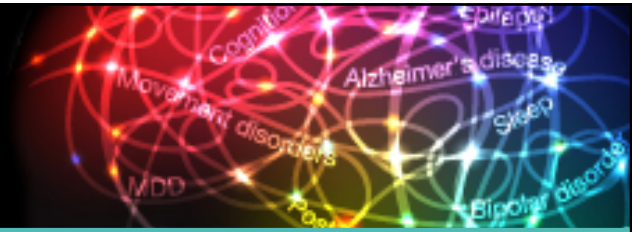
How to Choose a Medication



- Confirm the diagnosis of epilepsy
- Determine the seizure type
- Choose the most effective medication
- Consider comorbid conditions and side effects
- Determine speed of introduction
- Consider potential for compliance
- Assess cost and availability
- Mechanism of Action

Crepeau A, et al. *J Mayo Clin Proc.* 2017;92(2):306-318.

Frequency of Dosing



Once

- Eslicarbazepine
- Valproate extended release
- Oxcarbazepine extended release
- Phenytoin
- Phenobarbital
- Zonisamide
- Perampanel

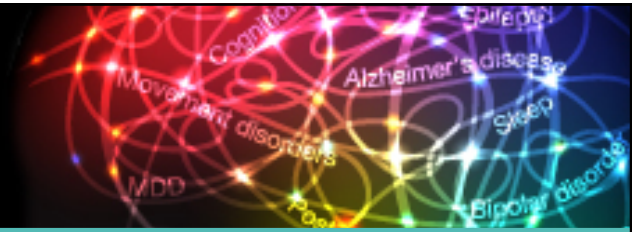
Twice

- Carbamazepine extended release
- Clobazam
- Levetiracetam
- Lamotrigine
- Lacosamide
- Topiramate
- Pregabalin
- Brivaracetam

Thrice

- Gabapentin
- Ezogabine

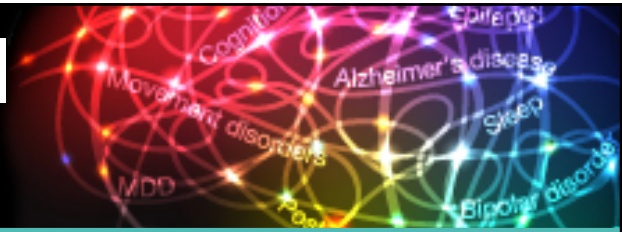
Extended-Release Antiepileptic Drugs



- Potential for once-daily dosing
- More stable mean drug concentration over time
- Improved tolerability profiles
- Possibility to achieve better seizure control and improve adherence

Uthman BM, et al. US Neurology. 2014;10(1):30-37.

Mechanism of Action- Rational Polypharmacy?



Na⁺ Channel

- Phenytoin
- Carbamazepine
- Oxcarbazepine
- Lamotrigine
- Lacosamide
- Rufinamide
- Eslicarbazepine

Glutamate Receptors

- Topiramate
- Zonisamide
- Perampanel
- Felbamate

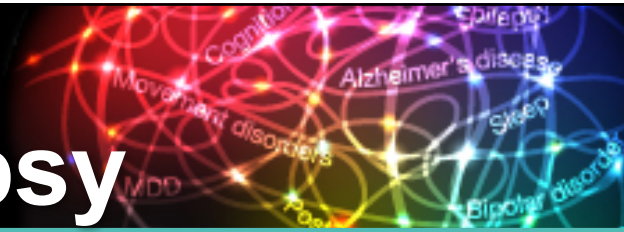
GABA

- Benzodiazepines
- Barbiturates
- Valproate
- Vigabatrin
- Tiagabine

Other

- Levetiracetam
- Ezogabine
- Gabapentin
- Pregabalin
- Ethosuximide
- Brivaracetam

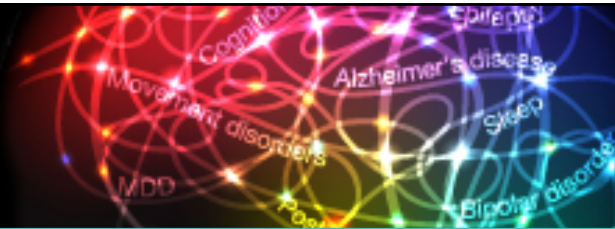
Rational Polytherapy for Treatment-Resistant Epilepsy



- Pharmacomechanistic approach to combining AEDs to achieve efficacy without increasing adverse event (AE) risk¹
- Combines drugs^{1,2}
 - With different mechanisms of action
 - Without complex pharmacokinetic interactions
 - Goal is to minimize pharmacodynamic interactions causing sedation, drowsiness, and other AEs
 - Without similar AE profile
 - In minimum doses to produce maximum effect
 - Newer AEDs have demonstrated efficacy as add-on therapy; many have improved AE profiles¹
 - Evidence supporting optimal combinations and guidelines for therapeutic decision-making remains limited^{1,2}

1. Brodie MJ, et al. *Seizure*. 2011-20:369-375; 2. Ben-Menachem E. *Epilepsia*. 2014;55(suppl 1):3-8₅

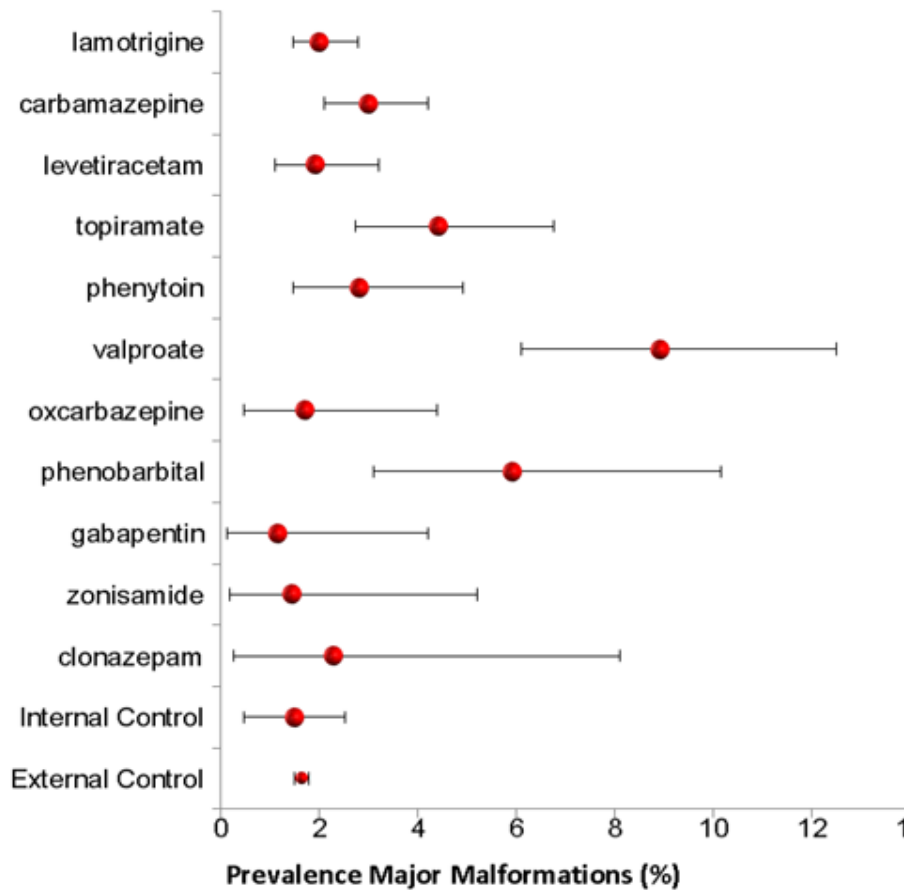
Pregnancy and Epilepsy



- Prevention
 - Women of child bearing age on prenatal vitamin
 - Contraception should be considered and AED interaction needs to be accounted for
- Incidence of seizures during pregnancy
 - About 2/3 of women remain seizure free during pregnancy
 - ~90% chance of seizure freedom during pregnancy if seizure free for 9 months prior to pregnancy
 - Breakthrough seizures can occur in greater incidence during 2nd and 3rd trimesters with lamotrigine

Battino D, et al. *Epilepsia*. 2013;54(9):1621-1627.
Harden CL, et al. *Neurology*. 2009;73(2):133-141.

Pregnancy Malformation With AEDs



N	%	95% CI
1994	2.1	(1.7 to 2.8%)
1094	3.0	(2.1 to 4.2%)
769	2.0	(1.1 to 3.2%)
451	4.4	(2.7 to 6.8%)
422	2.8	(1.5 to 4.9%)
336	8.9	(6.1 to 12.5%)
230	1.7	(0.5 to 4.4%)
202	5.9	(3.1 to 10.2%)
169	1.3	(0.14 to 4.2%)
136	1.5	(0.2 to 5.2%)
87	2.3	(0.3 to 8.2%)
532	1.5	(0.47 to 2.5%)
69277	1.6	(1.5 to 1.7%)

NAAED. <http://www.aedpregnancyregistry.org/wp-content/uploads/2016-newsletter-Winter-2016.pdf>

Efficacy, Safety and Tolerability of Lacosamide Monotherapy vs Controlled-Release Carbamazepine in Patients with Newly Diagnosed Epilepsy



- 74% of patients on LCM and 70% of patients on CBZ-CR completed 6 months of therapy seizure free
- Treatment emergent side effects leading to withdrawal occurred in 11% of those taking LCM and 16% of those taking CBZ-CR
- Treatment with LCM met non-inferiority criteria when compared with CBZ-CR and may be useful as first-line therapy for adults with newly diagnosed epilepsy

LCM = lacosamide, CBZ-CR = carbamazepine controlled release.
Baulac M, et al. *Lancet Neurology*. 2017;16:43-54.

Initiation of Antiepileptic Treatment in Patients with New Onset Epilepsy

- No differences between effectiveness, measured as seizure freedom and tolerability, have been demonstrated in comparative AED trials except for absence seizures.
- Selection of an AED for initial therapy can be guided by considerations other than relative efficacy (recognizing difference between focal and generalized seizures)
- Non-inferiority trials support monotherapy efficacy; superiority trials (unethical) or historical control trials (artificial) as currently required by FDA are not needed.
- All AEDs effective as adjunctive therapy appear to be effective as monotherapy

Use of Cannabidiol for Epileptic Encephalopathies



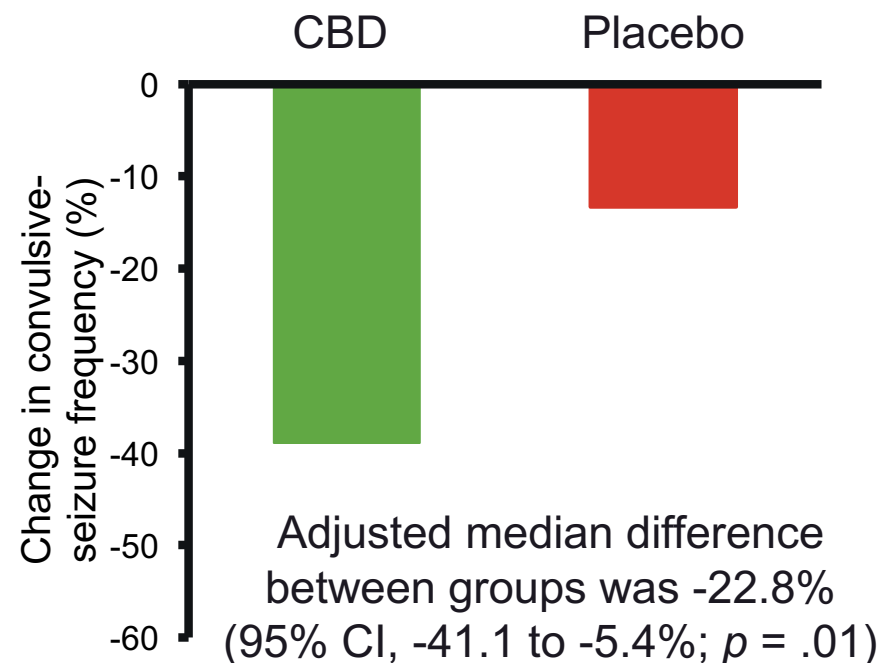
- Growing interest in CBD use for epileptic encephalopathies¹⁻⁴
 - CBD oil demonstrated efficacy in 3 clinical trials in Dravet syndrome and LGS, with 50% responder rates >35%²⁻⁴
- Questions remain regarding⁵
 - Efficacy in generalized epilepsy
 - Long-term safety and efficacy

CBD, cannabidiol; LGS, Lennox-Gastaut syndrome;

1. Friedman D, et al. *N Engl J Med*. 2015;373:1048-1058; 2. Devinsky O, et al. *Lancet Neurol*. 2016;15:270-278.
3. Devinsky O, et al. *N Engl J Med*. 2017;376:2011-2020; 4. Cross JH, et al. The American Epilepsy Society Annual Meeting; 2016; 5. Rosenberg EC, et al. *Neurotherapeutics*. 2015;12s:747-768.

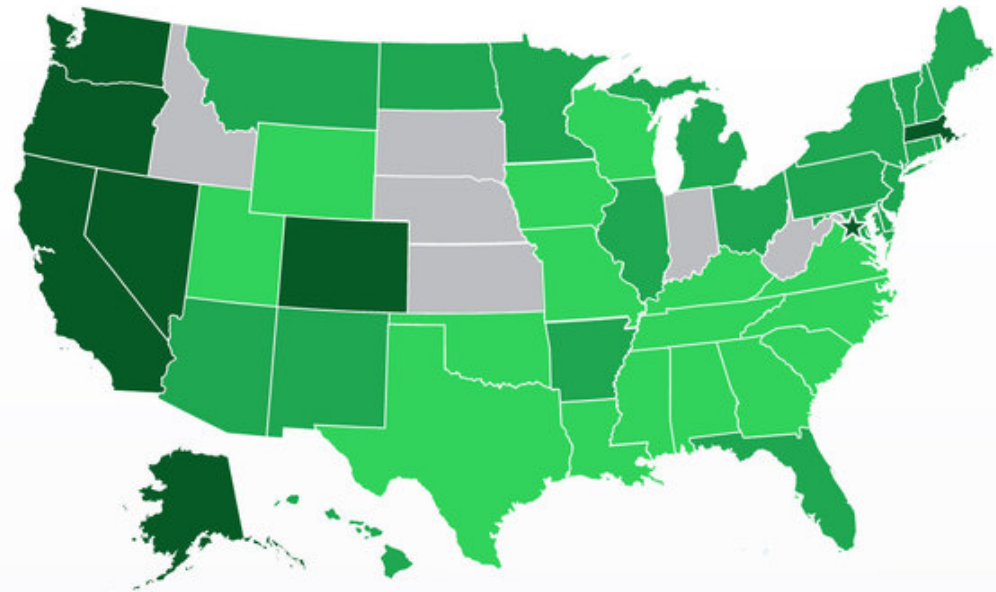
Efficacy of Oral CBD in Drug-Resistant Dravet Syndrome

- Randomized, double-blind, placebo-controlled trial
- Patients (ages 2-18 yrs) with Dravet syndrome and drug-resistant seizures (N = 120)
- CBD 20 mg/kg/day vs. PBO for 14 wks
- Primary endpoint: % change in convulsive-seizure frequency
 - CBD group: -38.9%, from 12.4 to 5.9 per month
 - PBO group: -13.3%, from 14.9 to 14.1 per month



Devinsky O, et al. *N Engl J Med.* 2017;376:2011-2020.

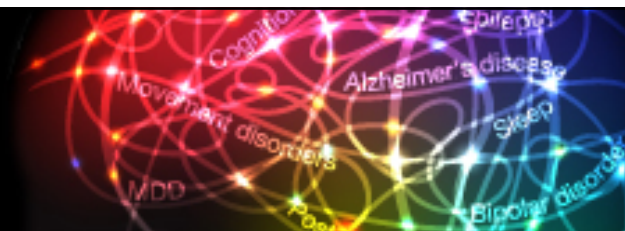
Medical Marijuana Laws- 2016



Recreational Marijuana	Medical Marijuana	Limited Medical Marijuana*
Alaska California Colorado Massachusetts Nevada Oregon Washington Washington, D.C.	Arizona Arkansas Connecticut Delaware Florida Hawaii Illinois Maine Maryland Michigan Minnesota	Alabama Georgia Iowa Kentucky Louisiana Mississippi Missouri North Carolina South Carolina Tennessee
	Montana New Hampshire New Jersey New Mexico New York North Dakota Ohio Pennsylvania Rhode Island Vermont	Texas Utah Virginia Wisconsin Wyoming

*Limited medical marijuana includes cannabis extracts that are high in cannabidiol and low in tetrahydrocannabinol
Fuller T. <https://www.nytimes.com/2016/10/25/us/marijuana-legalization-ballot-measures.html>

Call to Action



- Consider seizure type, comorbidities, drug characteristics, potential for compliance, and cost and availability of agents when selecting treatment for a patient with epilepsy
- If you should ever have questions, please visit
 - <https://www.epilepsy.com/learn/information-professionals>

Questions & Answers



Don't forget to fill out your evaluations to collect your credit.

