

The background of the slide features a close-up, high-angle view of an open book. The pages are fanned out, creating a series of curved, overlapping lines that lead the eye towards the center. A pencil is visible on the left side, and a pen nib is on the right side, both resting on the pages. The overall color palette is warm and muted, consisting of various shades of beige, cream, and light brown.

# CANNABIS THERAPY FOR PEDIATRIC EPILEPSIES

Bonni S. Goldstein, M.D.

Medical Director, Canna-Centers



**“There are many cases of so-called epilepsy in adults... in which India hemp (Indica/Kush) is the most useful agent with which I am acquainted”**

Dr. J. R. Reynolds *The Lancet* (1890)

**“Although the number of available antiepileptic drugs has increased substantially during the past 20 years, about a third of patients remain resistant to medical treatment.”**

Moshé, Solomon L., et al. "Epilepsy: new advances"  
*The Lancet* (2014)




# Pediatric Epilepsy

- Febrile Seizures
- Benign Rolandic Epilepsy (BECTS)
- Juvenile Myoclonic Epilepsy
- Dravet Syndrome
- Infantile Spasms (West's Syndrome)
- Lennox-Gastaut Syndrome
- Childhood Absence Epilepsy

- Benign Occipital Epilepsy
- Mitochondrial Disorders (i.e. MELAS and MERRF)
- Landau-Kleffner Syndrome (acquired epileptic aphasia)
- Rasmussen Syndrome
- Other structural, metabolic and genetic causes (hemimegalencephaly, lissencephaly, TS, Sturge-Weber, etc)

# Medically Refractory Seizures

**TABLE 2.** SUCCESS OF ANTIPILEPTIC-DRUG REGIMENS IN 470 PATIENTS WITH PREVIOUSLY UNTREATED EPILEPSY.

VARIABLE	No. (%)
<u>Response to first drug</u>	222 (47) 
Seizure-free during continued therapy with first drug	207 (44)
Remained seizure-free after discontinuation of first drug	15 (3)
<u>Response to second drug</u>	61 (13) 
Seizure-free during monotherapy with second drug	41 (9)
Remained seizure-free after discontinuation of second drug	20 (4)
<u>Response to third drug or multiple drugs</u>	18 (4) 
Seizure-free during monotherapy with third drug	6 (1)
Seizure-free during therapy with two drugs	12 (3)
Total	301 (64)

# Burden of Refractory Epilepsy

- ❑ Poor quality of life
- ❑ Side effects of medications
- ❑ Cognitive decline
- ❑ Injuries
- ❑ Psychosocial dysfunction
- ❑ Restricted lifestyle
- ❑ Increased mortality

# Side Effects of AEDs

- Lethargy/somnolence
- Loss of focus, learning, memory
- Anorexia, failure to thrive
- Loss of speech
- Loss of social skills
- Loss of motor skills
- Incontinence
- Insomnia
- Felbamate: aplastic anemia/liver failure
- Vigabatrin (sabril): permanent vision loss

***POOR QUALITY OF LIFE FOR WHOLE FAMILY!***

# Evidence of ECS Dysfunction in Epilepsy

- Blockage of the CB1 receptor produced status epilepticus (Wallace, et al. 2003, Deshpande, et al. 2007)
- Evaluation of epileptic human brain tissue removed surgically showed 60% deficiency of enzyme needed to produce 2-AG (Ludanyi, et al. 2008)
- Cerebrospinal fluid levels of endocannabinoids were found to be reduced in patients with untreated newly diagnosed temporal lobe epilepsy (Romigi, et. al. 2010)

# Literature Review

## 1978 Mechoulam et al

- 9 patients randomized to CBD 200 mg/day or placebo
- 2/4 CBD achieved sz freedom
- 0/5 placebo reported improvement
- No toxic side effects

## 1980: Cunha et al

- 16 refractory T-C sz pts
  - 8 received placebo/8 received CBD 200-300 mg/day
  - CBD group: 3 sz-free, 4 improved, 1 unchanged
  - Placebo group: 1 improved, 7 unchanged

## 1985: Ames et al

- 12 patients received CBD 200-300 mg/day or placebo
- No benefit; only side effect mild drowsiness



# Treatment with CBD in oily solution of drug-resistant pediatric epilepsies

Pelliccia et al: 2005 Congress on Cannabis and the Cannabinoids, Leiden, The Netherlands: IACM

Open Study of 18 pediatric patients with refractory seizure disorders treated with CBD

Authors concluded:

- No side effects of such a severity were observed as to require CBD discontinuation
- In most of the treated children, an improvement of the crises was obtained equal to, or higher than, 25% in spite of the low CBD doses administered
- In all CBD-treated children a clear improvement of consciousness and spasticity (whenever present) was observed

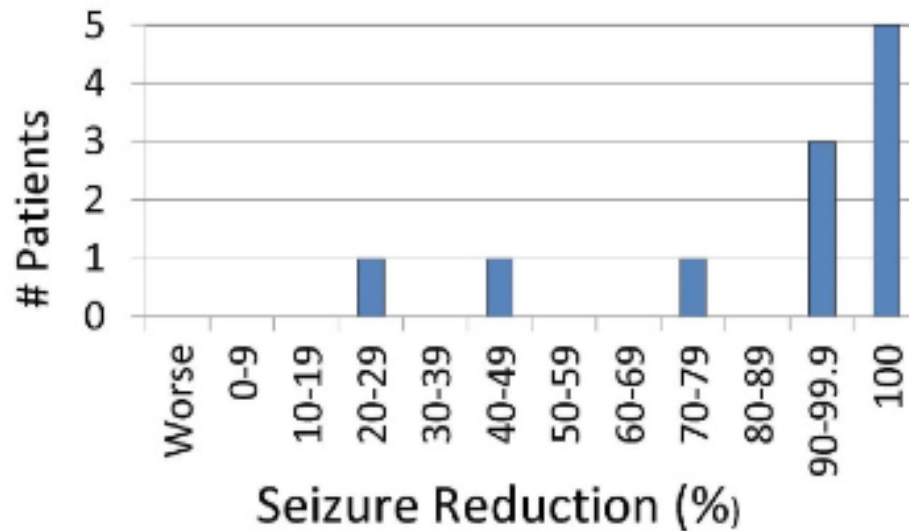
# Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

Porter B, Jacobsen C. *Epilepsy & Behavior* (2013)

- Survey of 19 patients using CBD-rich cannabis
- Thirteen children had Dravet syndrome, four had Doose syndrome, and one each had Lennox–Gastaut syndrome and idiopathic epilepsy
- Average number of antiepileptic drugs (AEDs) tried before CBD = 12
- **84%** (16/19) reported a reduction in their child's seizure frequency while taking cannabidiol-enriched cannabis
  - 11% (2/19) reported complete seizure freedom
  - 42% (8/19) reported a greater than 80% reduction in seizure frequency
  - 32% (6/19) reported a 25–60% seizure reduction
- Other beneficial effects included increased alertness, better mood, and improved sleep
- Side effects included drowsiness and fatigue

# Whole Cannabis Extract of High Concentration Cannabidiol May Calm Seizures in Highly Refractory Pediatric Epilepsies

Gedde and Maa: American Epilepsy Society, 67<sup>th</sup> Annual Meeting, December 10, 2013



**Reduction in Weekly Seizures at Three Months of High Concentration Cannabidiol Extract (Realm Oil) Therapy**

- ❑ 73% report 98-100% reduction of seizures
- ❑ At 3 months, 45% seizure free

**Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox-Gastaut Syndrome.** Hussain, S.A. et al. *Epilepsy & Behavior* (April 2015)

- 117 parents of children with epilepsy (including 53 with IS or LGS) who had administered CBD products to their children
- 85% reported seizure reduction
- 14% reported complete seizure freedom
- Average # of AEDs tried: 8
- 30% reported increased appetite
- 53% improved sleep; 71% improved alertness; 63% improved mood
- “Extraordinarily vulnerable to participation bias and limited by lack of blinded outcome ascertainment”

# CBD Anticonvulsant Mechanisms of Action

Thought to be due to combination of beneficial effects stacking upon one another (polypharmacology)

- Receptor-independent channels
- Binds or blocks non-cannabinoid receptors thereby modulating neurotransmitter excitation
  - Blocks NMDA receptor
  - Binds to GABA receptors
- Modulates ion channels
  - Modulates BK (potassium) channels in neurons
  - Modulates calcium release in neurons
- Blocks uptake of EC thereby enhancing/normalizing EC levels
- Anti-inflammatory (inflammatory reactions in brain can enhance neuronal excitability and impair cell survival )
- Neuroprotective/anti-oxidant (reduced oxidative stress/glutamate toxicity)

# CBD Anticonvulsant Mechanisms of Action

- CBD blocks NMDA receptor
  - similar mechanism as Felbamate
- CBD enhances GABA receptor
  - similar mechanism as Felbamate, Depakote, Tegretol, Onfi, Phenobarbital
- CBD stabilizes ion channels
  - similar mechanism as Banzel, Lamictal, Dilantin, Keppra, Trileptal

# CBD and AED overlap

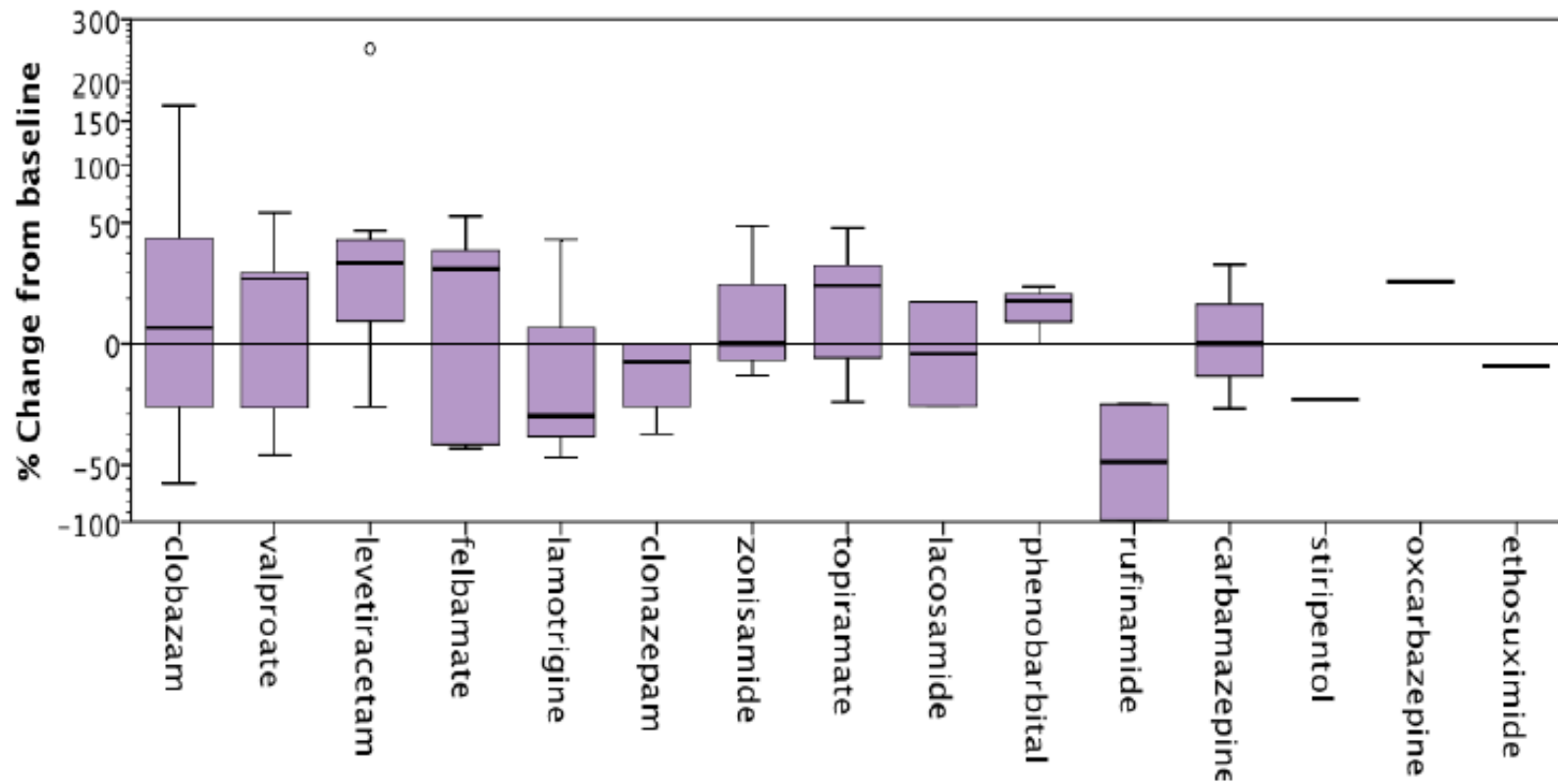
CBD actions:	X?	✓	✓	✓	✓	✓	✓	?	?
	Voltage-gated Na <sup>+</sup> channels	HVA Ca <sup>2+</sup> channels	LVA Ca <sup>2+</sup> channels	Voltage-gated K <sup>+</sup> channels	GABA <sub>A</sub> receptors	GABA Turnover	Glutamate receptors	Synaptic vesicle protein 2A	Carbonic anhydrase
Phenobarbital		+			+++		+		
Phenytoin	+++								
Ethosuximide			+++						
Carbamazepine	+++								
Sodium valproate	++		++			++			
Benzodiazepines					+++				
Vigabatrin						+++			
Lamotrigine	+++	++					+		
Gabapentin	+	++							
Felbamate	++	++			++		++		
Topiramate	++	++		+	++		++		+
Tiagabine						+++			
Oxcarbazepine	+++								
Levetiracetam		+			+			+++	
Pregabalin		++							
Zonisamide	+++		++						+
Stiripentol					+++				
Rufinamide	+++								
Lacosamide	+++								+
Eslicarbazepine acetate	+++								
Retigabine				+++					
Perampanel							+++		

Neurosci Lett. 2014 Apr 30;566:269-74. doi: 10.1016/j.neulet.2014.03.013. Epub 2014 Mar 16.

**Voltage-gated sodium (NaV) channel blockade by plant cannabinoids does not confer anticonvulsant effects per se.**

Hill AJ<sup>1</sup>, Jones NA<sup>1</sup>, Smith I<sup>2</sup>, Hill CL<sup>1</sup>, Williams CM<sup>3</sup>, Stephens GJ<sup>2</sup>, Whalley BJ<sup>4</sup>.

# CBD - AED interaction



Friedman, et al. The effect of Epidiolex (cannabidiol) on serum levels of concomitant anti-epileptic drugs in children and young adults with treatment-resistant epilepsy in an expanded access program. American Epilepsy Society. Seattle, WA2014.



# Requirements for CBD Oil

- Concentrated
  - For example, 50 mg/ml, 100 mg/ml, 200 mg/ml
- Consistent in strain
  - Different strains (even if high CBD) can wreak havoc in epilepsy patients
- Tested
  - Potency, pesticides, terpenoid profile, mold/microbes, residual solvent (if used)
- Affordable
  - 5¢ per mg - 50¢ per mg
- Reliable supply
  - Patients who start treatment may wean other medications
  - Catastrophic if oil not available and weaned AEDs

# Cannabidivarin (CBDV) and THCA

**Cannabidivarin is anticonvulsant in mouse and rat** Hill, AJ et al. British Journal of Pharmacology December 2012

**Cannabidivarin-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism** Hill, TD et al. British Journal of Pharmacology October 2013

**Nonpsychotropic Plant Cannabinoids, Cannabidivarin (CBDV) and Cannabidiol (CBD), Activate and Desensitize Transient Receptor Potential Vanilloid 1 (TRPV1) Channels in Vitro: Potential for the Treatment of Neuronal Hyperexcitability** Iannotti, FA et al. ACS Chemical Science July 2014

- Many patients in California are using THCA oil in addition to CBD oil with enhancement of seizure reduction
- CBDV research ongoing and may be available soon

# Results from California medical cannabis practice

- Criteria:
  - ▣ Diagnosis of Intractable Epilepsy
  - ▣ At least three month trial with same high CBD oil
  - ▣ Oil tested at reputable cannabis lab
  - ▣ Neurologist aware of plan
  
- 112 patients aged 1 – 44 years of age
- 15 of 112 (13%) were not on AEDs
- Avg number of AEDs tried and failed: 12
- Strains: AC/DC, Charlotte's Web, others
- Terpenoid profile: high in  $\beta$  caryophyllene,
- CBD:THC ratio: 15:1 up to 31:1 (one patient at 6:1)

# Results from California medical cannabis practice

112 patients with the following diagnoses:

<b>DIAGNOSIS</b>	<b># OF PATIENTS</b>
Cryptogenic	37
Genetic Causes	16
Lennox-Gastaut Syndrome	13
Congenital Brain Malformations	9
Dravet Syndrome	8
Birth Trauma	7
Infantile Spasms	4
Metabolic Syndromes	4
Encephalitis	3
Absence Seizures	3
Aicardi Syndrome	3
Doose Syndrome	2
Other Syndromes	2
Tuberous Sclerosis	1

# Results from California medical cannabis practice

<b>No Response</b>	11/112	10%
<b>No Reduction in # of seizures but reduction in severity /duration</b>	18/112	16%
<b>25-49% reduction of seizures</b>	10/112	9%
<b>50-74% reduction of seizures</b>	18/112	16%
<b>75-99% reduction of seizures</b>	42/112	38%
<b>Seizure Free</b>	13/112	12%

**Overall 75% of patients had > 25% reduction of seizures**

# Results from California Medical Cannabis practice

	Cryptogenic	Infantile Spasms	Genetic	Metabolic Syndromes	Encephalitis	Tuberous Sclerosis	Birth Trauma	Absence Seizures	Congenital Brain Malformations	Aicardi Syndrome	Doose Syndrome	Dravet Syndrome	LGS	Other syndromes
No Response	5	1	2						1				2	
No Change in # of SZ	7	2	2	1	1					1		2	1	1
25-49% Seizure Reduction	1		2				2			1	1	2		
50-74% Seizure Reduction	7						2	2	2	1	1		3	
75-99% Seizure Reduction	12	1	9	2	2	1	1	1	4			3	7	
Seizure Free	5		1	1			2		2			1		1

**Genetic Syndromes include:** SCN8A, EHMT1, Dup5Q, Rett Syndrome (MECP2), Nieman Pick C (SMPD1), KCNQ2/3, SYNGAP1, Down Syndrome, Mowat-Wilson (ZEB2), CDG1K

**Congenital Brain Malformations include:** Lissencephaly, Schizencephaly, Cortical Dysplasia, Pachygyria

**Other Syndromes include:** Parry-Romberg Syndrome and Smith-Magenis Syndrome

# Results from California medical cannabis practice

- 10/13 Seizure Free patients were able to wean one or more AEDs
  - 5/13 (38%) are pharmaceutical free!
- 14/42 patients with 75-99% reduction were able to wean off one or more AEDs
  - 7/42 (17%) are pharmaceutical free!
- 8/18 patients with 50-74% reduction were able to wean off one or more AEDs

**Overall 29% able to wean one or more AEDs**

**Overall 11% pharmaceutical-free**

# Results from California medical cannabis practice

## Beneficial Side Effects reported by parents:

- ▣ More alert and aware
- ▣ More energy/endurance for therapy and play
- ▣ Better sleep
- ▣ Better mood, happier, smiles more
- ▣ Better speech
- ▣ Better appetite
- ▣ More opinionated, able to argue
- ▣ Improved focus and memory
- ▣ Improved balance and coordination
- ▣ No emergency room visits or hospitalizations
- ▣ Two patients with Type 1 DM – more stable glucose levels



# Results from California medical cannabis practice

## Negative side effects reported by parents

- ▣ Decreased sleep (3 patients)
- ▣ Diarrhea (4 patients)

## Reasons 11 patients who reported failed treatment

- ▣ 6 reported worsening of seizures
- ▣ 1 mother stopped oil because 19 yo patient was noncompliant
- ▣ 4 reported too expensive and not improved