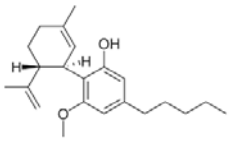
# Cannabinoids and Epilepsy

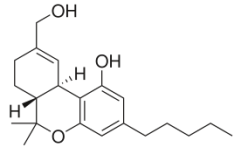
Michael Ciliberto, MD
University of Iowa
Stead Family Department of Pediatrics

# Cannabinoids

- Cannabinoids= terpenophenolic compounds (give a scent)
- **>80** in Cannabis sativa
- Cannabidiol (CBD) isolated in 1940



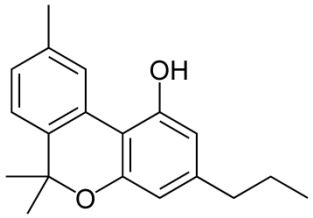

- Delta-9-Tetrahydrocannabinol (THC)= psychoactive- (Isolated and characterized in 1964)



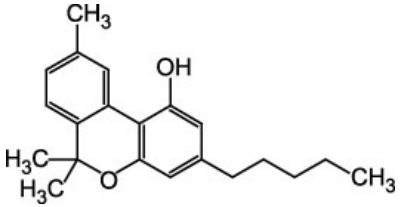

- 1980s :THC binds to CB1 (mostly central nervous system) and CB2 (mostly peripheral receptors) receptors

# Other cannabinoids in the cannabis plant

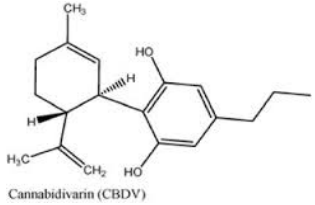
- Cannabivarin




- Cannibinol

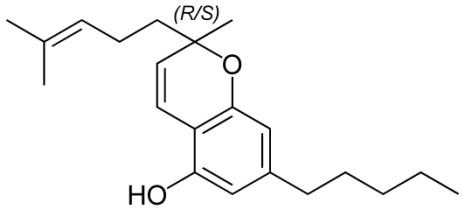



- Canabidivarin



Cannabidivarin (CBDV)

- Cannabichromene

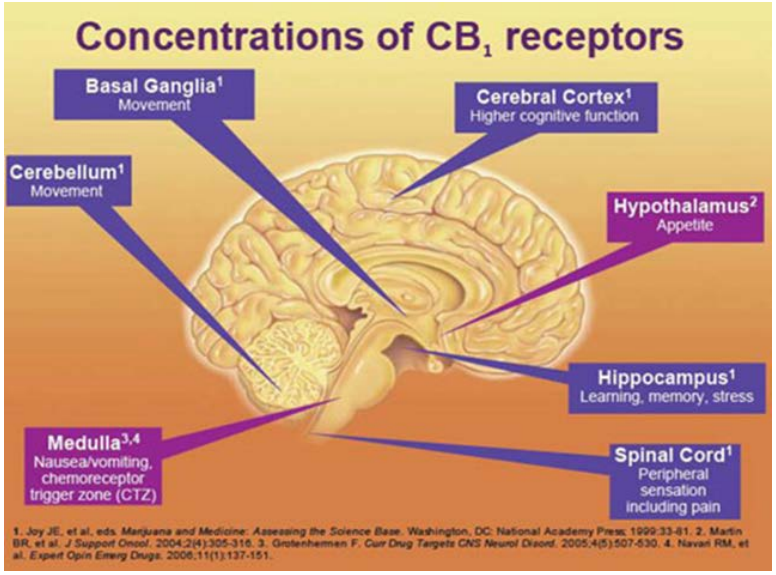


# Distribution and elimination

- Highly liposomal- Vd=32L/kg- highly distributed to brain, adipose tissue
- May accumulate in a depot form in patients with high adiposity
- Metabolized in the liver
- Hydroxylated to 7-OH-CBD by cytochrome P450 enzymes(CYP3A/CYP2C)
- Most excretion through feces
- Terminal T1/2= 18-32 hrs

# CB1 and CB2 receptors

CB1 receptors




-Decreases glutamate release
-Effects neuronal growth and migration

CB2 receptors

- Periphery
- Immune system
- Hematopoietic cells
- GI system
- Cardiac system
- Skeletal system

**Table 2. (A) Proposed molecular targets for plant cannabinoids investigated in animal models of seizure and (B) Cannabinoid efficacy in animal models of seizure and epilepsy**

| Cannabinoid | Molecular target(s) |
|---|---|
| *(A)* | |
| $\Delta^9$-Tetrahydrocannabinol ($\Delta^9$-THC) | CB1R, CB2R, TRPV1, TRPV2 |
| $\Delta^9$-Tetrahydrocannabivarin ($\Delta^9$-THCV) | CB1, CB2, TRPV1, TRPV3, TRPV4 |
| Cannabidiol (CBD) | ENT, GPR55, TRPV1, TRPV2, TRPV3, TRPA1, FAAH, TRPM8, adenosine, $5HT1_A$ |
| Cannabidivarin (CBDV) | TRPV4, DAGL$\alpha$ |
| Cannabinol (CBN) | CB1R, TRPV4, TRPA1 |

| Plant cannabinoid | Model | Efficacy |
|---|---|---|
| *(B)* | | |
| $\Delta^9$-Tetrahydrocannabinol ($\Delta^9$-THC) | Generalized seizure (e.g., MES, PTZ, 6 Hz, 60 Hz, nicotine, and strychnine) | Y |
| | Temporal lobe epilepsy | Y |
| Synthetic CB1R agonists (e.g., WIN55-212) | Generalized seizure (MES, PTZ, amygdala kindling) | Y |
| | Partial seizure with secondary generalization (penicillin and maximal dentate gyrus activation) | Y |
| | Temporal lobe epilepsy | Y |
| | Absence epilepsy (WAG/Rij) | Mixed effect |
| Synthetic CB1R antagonists (e.g., SR141716A) | Generalized seizure (MES and PTZ) | N[a] |
| | Absence epilepsy (WAG/Rij) | N |
| | Partial seizures with secondary generalization (penicillin but not maximal dentate gyrus activation) | N[a] |
| | Epileptogenesis (juvenile head trauma but not kainic acid) | Y |
| $\Delta^9$-Tetrahydrocannabivarin ($\Delta^9$-THCV) | Generalized seizure | Y |
| Cannabidiol (CBD) | Generalized seizure (MES, PTZ, 6 Hz, 60 Hz, picrotoxin, isonicotinic acid, bicuculline, hydrazine, limbic kindling (electrical), and strychnine but not 3-mercaptoproprionic acid) | Y |
| | Temporal lobe convulsions/status epilepticus | Y |
| | Partial seizures with secondary generalization (penicillin but not cobalt) | Y |
| Cannabidivarin (CBDV) | Generalized seizure (MES, PTZ, and audiogenic) | Y |
| | Temporal lobe convulsions/status epilepticus | Y |
| | Partial seizures with secondary generalization (penicillin only) | Y |
| Cannabinol (CBN) | Generalized seizure (MES only) | Y |

[a]Indicates a proconvulsant effect.

# Cannabidiol MOA

- Activates Transient receptor potential channels (TRP)-voltage gated ion channels for Mg, Na, Ca; works on TRPV1 (activate/desensitize), TRPV2, TRPA1, CBDV too
- G-protein coupled receptors (GPR) alter Ca conduction et al.
- Adenosine receptor modulator & reuptake inhibitor

# MOA CBD

- **Low-sub micromolar levels**

  **Blocks** the transport of stimulating neurotransmitters into the cell, alters Ca permeability;

  **Activates** 5HT-1a receptor agonist, alpha1 (serotonin pathway) and alpha 3 glycine receptors,

  **Activates** inhibits cellular uptake and degradation of anandamide (endogenous cannabinoid)

  **Reduces the psychoactive effects of THC and enhances therapeutic window of THC likely secondary to CB1 antagonism**

# MOA continued

- A recent study by Patel et al. notes that CBD inhibits aberrant sodium currents in mutated $Na_v1.6$ channels
- Also noted were changes in sodium mediated currents of other types
- T-type Ca channel antagonist

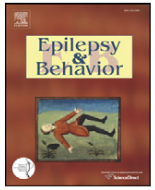
The Stanford questionnaire
150 parents in group
19 replied

Epilepsy & Behavior 29 (2013) 574–577

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh




Brief Communication

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

Brenda E. Porter, Catherine Jacobson *

[a] *Department of Neurology, Stanford University, USA*

**Table 1**
Summary of survey responses.

| Patient | Diagnosis | Age and sex | Age at seizure onset | Time on CBD | CBD (mg/kg/day) | THC (mg/kg/day) | Seizures before CBD | Seizures after CBD | Estimated change in seizure frequency | Number of AEDs tried before CBD | AEDs discontinued while on CBD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | LGS | 7 y, female | <1 y | >1 y | ? | ? | >100/day | 8–10/day | >−80% | 8 | Banzel, Onfi |
| 2 | DS | 14 y, female | <1 y | >4 m | 14 | 0.5 | 5/day | 0–1/day | >−80% | 12 | |
| 3 | EFMR | 12 y, female | <1 y | 2–4 m | 7 | 0.5 | 12/day | 0–1/day | >−80% | 17 | |
| 4 | DS | 7 y, male | <1 y | >4 m | 8 | 0.25−0.5 | 50/week | 50/week | 0 | 16 | |
| 5 | DS | 6 y, female | <1 y | >4 m | 4 | 0.1–0.25 | 200–300/week | 0–2/week | >−80% | 6 | Onfi |
| 6 | DS | 16 y, female | <1 y | >4 m | 1–2 | 0.02–0.1 | 7/week | 4/week | −25% | 16 | Onfi |
| 7 | DS | 13 y, male | <1 y | 3–4 m | 4 | 0.02–0.1 | 40/week | 30/week | −25% | 16 | Phenobarbital, Depakote |
| 8 | DS | | <1 y | >4 m | ? | ? | 3/week | 1–2/week | −50% | 14 | Klonopin |
| 9 | DS | Male | <1 y | >4 m | 3–4 | 0.04–0.2 | 100–500/week | 1–2/week | >−80% | 10 | STP, Topamax, Depakote |
| 10 | DS | | <1 y | >4 m | 4 | 0.2–0.4 | 200–300/week | 20–50/week | >−80% | 12 | STP |
| 11 | DS | 8 y, female | <1 y | >1 y | ? | ? | 5–10/week | 0–3/week | −60% | 10 | STP, Onfi, Depakote |
| 12 | DS | 7 y, female | <1 y | >4 m | 3–4 | 0.04–0.2 | 20+/week | 0–10/week | −50% | 10 | Onfi, Zonegran, Depakote |
| 13 | Doose | 9 y, female | <1 y | >4 m | 10–13 | 0.5 | 60–250/day | 0 | >−80% | 15 | Lorazepam, ethosuximide |
| 14 | DS | 2 y, male | <1 y | >4 m | 7 | 0.08–0.4 | 2/week | 0 | >−80% | 4 | |
| 15 | Doose | | 2–5 y | 2 w | <0.5 | 0.01–0.05 | 1–7/week | 1–7/week | 0 | 13 | |
| 16 | Doose | 11 y, male | 2–5 y | 1–2 m | 6 | 0.6–0.8 | 20/week | 4/week | >−80% | 13 | |
| 17 | Doose | | 2–5 y | 1–2 m | 6 | 0 | 15–20/day | 0–3/day | >−80% | 14 | Steroids |
| 18 | Idiopathic | Female | 1–2 y | <1 m | 28 | 0.5–0.7 | 10/week | 8/week | −25% | 5 | Valproic acid |
| 19 | DS | 6 y, female | <1 y | >4 m | 1 | 0.06–0.3 | 3/week | 3/week | 0 | ? | |

LGS, Lennox–Gastaut syndrome; DS, Dravet syndrome; EFMR, epilepsy in females with mental retardation; STP, stiripentol; y, year/years; m, month/months; w, weeks.

# Cannabinoids for epilepsy (Review)

Gloss D, Vickrey B

THE COCHRANE COLLABORATION®

- Cannabinoids for epilepsy (Review)
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| Study authors | Number of patients | Drug received | Patient characteristics | Primary outcome= seizure freedom | Follow up period | results |
|---|---|---|---|---|---|---|
| Cunha 1980 | 15 | 200-300 mg CBD/ day | TLE with sec gen; 1sz/wk | Not mentioned | 41/2 months | No toxicity 4/8 patients= nearly sz free 1= no effect |
| Mechoulam 1978 | 9 4 received CBD | 200 mg CBD | | NM | 3 months | 2/4= seizure free for 3 months |
| Trembly 1990 | 12 pts 10 reported on | 300 mg CBD | | | ? 12 months | No change in 10 pts |
| Ames 1985 | 12 pts | 300 mg then 200 mg | | | 1 month | No change in sz freq |

# Recent Data

- Devinsky et al. (Lancet Neurology)
- 1-30 years of age
- Titration to 25mg/kg/d of CBD from GW
- Enrolled 214 pts
- Withdrawal secondary to liver problems, sesame oil allergy, somnolence, GI side effects, worsened seizures, inc. ammonia
- 39% had >50% seizure reduction, 21% >70%, 9% >90%

| | Safety group (n=162) | Efficacy group (n=137) |
|---|---|---|
| Dravet syndrome | 33 (20%) | 32 (23%) |
| Lennox-Gastaut syndrome | 31 (19%) | 30 (22%) |
| Other | 27 (17%) | 24 (18%) |
| Unknown | 14 (9%) | 8 (6%) |
| Minimal brain dysfunction | 13 (8%) | 10 (7%) |
| CDKL5 mutation | 8 (5%) | 8 (6%) |
| Tuberous sclerosis complex | 6 (4%) | 3 (2%) |
| Aicardi syndrome | 6 (4%) | 5 (4%) |
| Epilepsy with myoclonic absences | 5 (3%) | 3 (2%) |
| Myoclonic-astatic ep (Doose s/d) | 5 (3%) | 5 (4%) |
| FIRES | 3 (2%) | 1 (<1%) |
| dup15q disorders | 3 (2%) | 3 (2%) |
| Ohtahara syndrome | 2 (1%) | 2 (<1%) |
| Neuronal ceroid lipofucinosis | 2 (1%) | 0 |
| Jeavons syndrome | 2 (1%) | 1 (<1%) |
| Down syndrome | 1 (<1%) | 1 (<1%) |
| Autoimmune | 1 (<1%) | 1 (<1%) |

Data are n (%).

# Dravet CBD

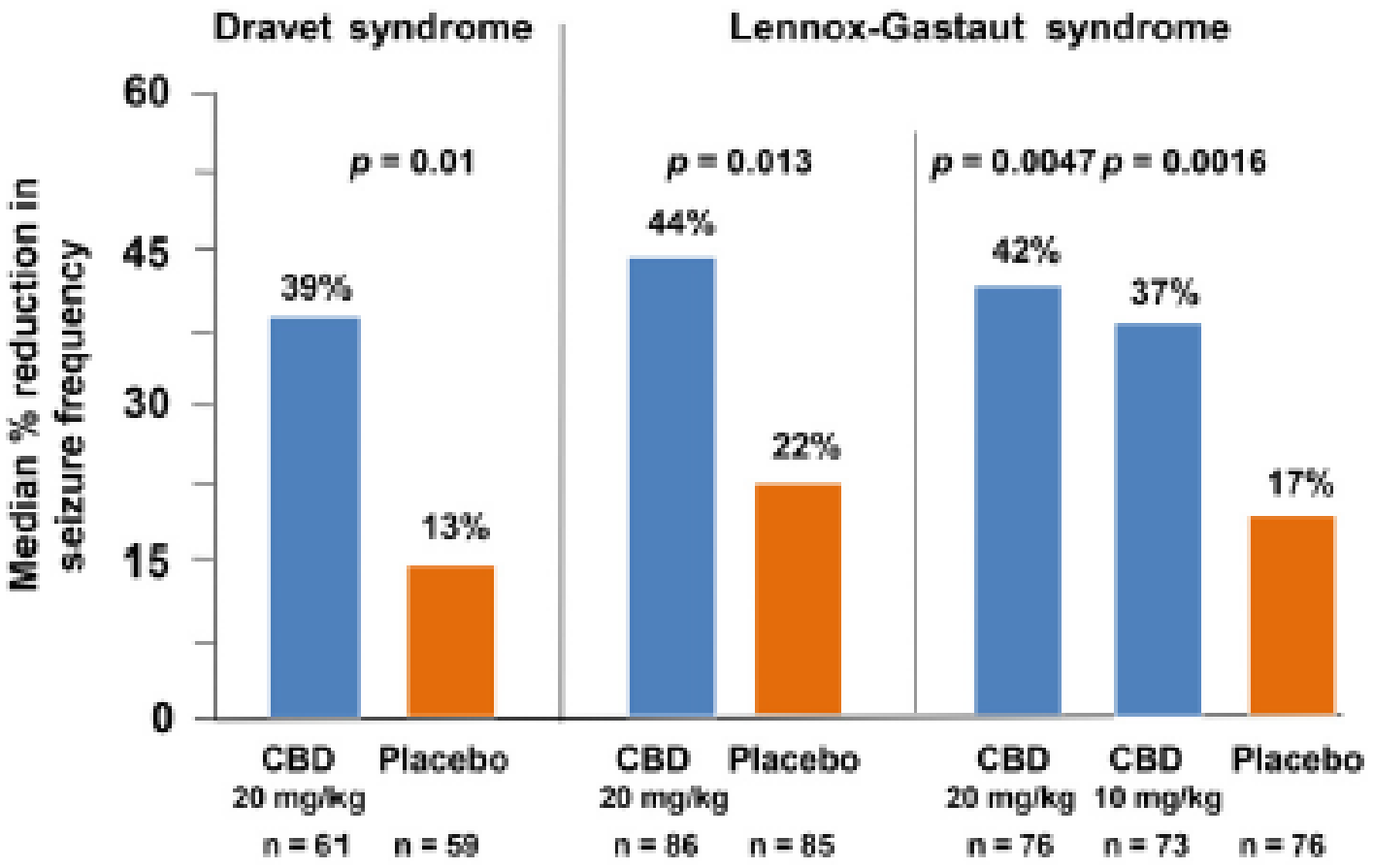
- 2-18yo
- Median change in szs/mo -38.9% vs -13.3%
- Responders 43% vs 27%
- Dec appetite, diarrhea, sedation, inc AST/ALT

N Engl J Med. 2017 May 25;376(21):2011-2020. **Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome.** Devinsky O[1], Cross JH[1], Laux L[1], Marsh E[1], Miller I[1], Nabbout R[1], Scheffer IE[1], Thiele EA[1], Wright S[1]; Cannabidiol in Dravet Syndrome Study Group.

# LGS CBD

- 2-55yo
- 2 drops per week
- Freq of drop dec by 43.9% vs 21.8%
- Responder rate 44% vs 24%
- Monthly freq of szs dropped by 41.2% vs 13.7%
- >10%: diarrhea, sedation
- 12 w/drawals 3 for inc ALT/AST

Lancet. 2018 Mar 17;391(10125):1085-1096.**Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial.**




- Perucca E. J Epilepsy Res. 2017 Dec 31;7(2):61-76. **Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last?**

# Efficacy in other epilepsies

- Case report of unilateral cortical dysplasia becoming seizure free on pure CBD after side effects on commercial medical MJ (Crippa et al. Δ9-THC Intoxication by Cannabidiol-Enriched Cannabis Extract in Two Children with Refractory Epilepsy: Full Remission after Switching to Purified Cannabidiol. Front Pharm 2016 Sep 30; 7. 359)
- Case series of seven pts in Fever infection-related epilepsy syndrome (FIRES) (Gofshteyn et al. Cannabidiol as a Potential Treatment for Febrile Infection-Related Epilepsy Syndrome (FIRES) in the Acute and Chronic Phases. J Ch Neuro 2016 Sep 21)
- Case series of 18 pts with tuberous sclerosis complex (Hess et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. Epilepsia. 2016 Oct;57(10):1617-1624.)
- Case series of 4 pts with Sturge-Weber syndrome (**Cannabidiol** Treatment for Refractory Seizures in Sturge-Weber Syndrome. Kaplan EH, Offermann EA, Sievers JW, Comi AM. Pediatr Neurol. 2017 Feb 22. Epub)
- Striking absence of data in:
  - Childhood absence epilepsy
  - Juvenile myoclonic epilepsy
  - Most focal epilepsies

# Drug interactions

- Increased levels of clobazam & desmethyl-clobazam
- Slight increases in topiramate, rufinamide, and eslicarbazepine


- Geffrey AL, et al. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia 2015;56:1246-51.
- Gaston TE, et al.; UAB CBD Program. Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia 2017;581586-92.


- Increased risk of elevated liver enzymes with coadministration of valproic acid

# Data for artisanals

- Retrospective assessment of 272 patients noted:
  - 37 (14%) ineffective,
  - 29 (15%) experienced a 1-25% reduction,
  - 60 (18%) experienced a 26-50% reduction,
  - 45 (17%) experienced a 51-75% reduction,
  - 75 (28%) experienced a 76-99% reduction in seizures,
  - 26 (10%) experienced a complete clinical response.

– Sulak et al. Epilepsy and Behav. 2017 May;70(Pt B):328-333 The current status of artisanal cannabis for the treatment of epilepsy in the United States.

# Concerns regarding artisanals

- Batch to batch variation
- Drug interactions
- Inability to reach high doses of cannabinoids proven to be efficacious secondary to side effects
- Treatment stagnation
- Non-medical personnel making dosing and treatment recommendations without rigorous data