Cannabidiol for Epilepsy

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Knowledge that will change your world

Disclosures

- Salary support from State of AL Department of Commerce funded CBD program through "Carly's Law"
- I (via PI Jerzy Szaflarski, MD, PhD) prescribe CBD to patients with epilepsy through the UAB CBD Program

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Perspective

- In the US, ~3M people have epilepsy
  - ~1M are medically intractable despite best medical and surgical treatment
- ~Worldwide, ~70M people have epilepsy
  - ~20M medically intractable
- Intractable epilepsy is under-recognized and under-treated
- New treatments are desperately needed
  - Is there a role for *Cannabinoids*?

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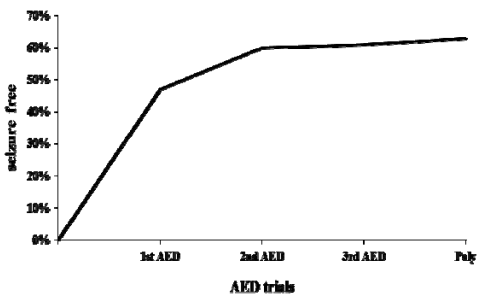
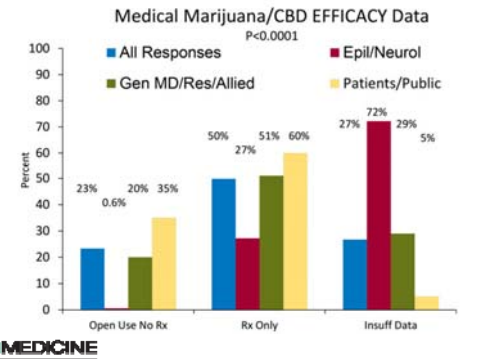
Englot et al., 2012, Neurology

Diminishing returns with AEDs



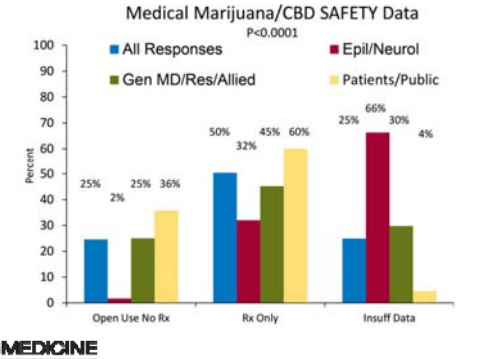
Kwan and Brodie NEJM 2000;342:314-9

Efficacy of Cannabis for epilepsy Tx



Mathern et al., 2015 Epilepsia

Safety of Cannabis for epilepsy Tx



Mathern et al., 2015 Epilepsia

Phytocannabinoids' Pharmacology

- Δ 9- THC
  - Main psychoactive component of *cannabis* plant
  - Best studied target is endocannabinoid receptors – CB1 and CB2
  - CB1 (and lesser extent CB2) expressed in pre-synaptic terminals in CNS, G-protein coupled receptor which modulates neurotransmitter release
  - Reduces hyperexcitability
- Cannabidiol (CBD)
  - No psychoactive properties
  - Low affinity for endocannabinoid receptors
  - Specific mechanism by which exerts anti-convulsant effects is unknown
- Both compounds are very lipophilic

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Wallace et al., 2003, J Pharmacology and Exp Therapeutics
Gaston et al., 2017 Epilepsy and Behavior

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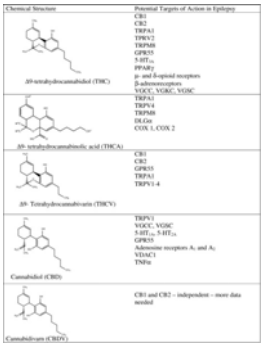
Cannabinoids and Epilepsy



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Gaston et al., 2017 Epilepsy and Behavior

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Animal Model Data

- THC, CBD,THCA, THCV, and CBDV have all demonstrated efficacy in seizure/epilepsy models in rats

(Hill et al. 2010 Epilepsia, Wallace et al. 2002 Eur J Pharmacology, Wallace et al. 2003 J Pharmacol Experimental Therapy)

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CBD – DOES IT WORK IN HUMANS?

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Summary of efficacy data prior to 2015

Author (reference)	Number of participants	Age of participants	Diagnosis	Preparation	Dosage	Response
Ames and Cridland [60]	12*	Adults	Epilepsy and MR	CBD capsules	Up to 600 mg/day	–
Cunha et al. [61]	15*	Adults	Focal-onset epilepsy	CBD capsules	~1.5 mg/kg/day	4/8 CBD and 1/8 placebo improved
Davis and Ramsey [62]	5	Children	Epilepsy and MR	THC isomers	Up to 4 mg/day	2/5 improved and 1/5 worsened
GW Pharma [57]	27	Children and adults	Epilepsy	CBD (Epidiolex)	–	13/27 improved 50% or more
Lorenz [63]	6*	Children	Epilepsy and MR	THC	Up to 0.12 mg/kg/day	4/6 improved
Mechoulam and Carlini [64]	9*	Adults	Temporal lobe epilepsy	CBD	200 mg/day	3/4 CBD and 0/5 placebo improved
Porter and Jacobson [65]	19*	Children	Catastrophic epilepsies	CBD/THC	CBD up to 28 mg/kg/day THC up to 0.8 mg/kg/day	16/19 improved
Trembly and Sherman [66]	12*	Adults	Epilepsy	CBD	300 mg/day	–

- 69/102 patients received Cannabis products
- 42/69 were "responders" (61%)
- Cochrane Review – "no reliable conclusions can be drawn … regarding the efficacy of cannabinoids for the treatment of epilepsy" (Gloss and Vickerey, 2014)

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Szaflarski & Bebin, 2014 EB

Porter and Jacobson, 2015

- Survey or parents of children treated at Stanford who used THC/CBD products for seizure control (Facebook)
- 84% reported improvement:
  - 11% seizure free
  - 42% >80% seizure reduction

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	7	7	>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	EPMR	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	0/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	?	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	7	?	5–10/week	0–1/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	Dravet	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	0.04–0.4	2/week	0	>−80%	4	
15	Dravet		2–5 y	2 w	<0.5	0.01–0.05	1–7/week	1–7/week	0	13	
16	Dravet	11 y, male	2–5 y	1–2 m	6	0.6–0.8	20/week	4/week	>−80%	13	
17	Dravet		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	0.04–0.3	3/week	3/week	0	7	

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CBD Programs

- Expanded Access Programs (EAPs)- compassionate use, generally state funded. All open label.
  - UAB CBD Program
- Several Phase 3 placebo-controlled clinical trials are ongoing/in data analysis (Dravet, LGS, TSC)
- Product used – Epidiolex® (Greenwich Biosciences) < 1% THC content

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UAB CBD Program

- Funded by State of AL "Carly's Law"
- Adult and Pediatric arms
- Must have failed at least 4 AEDs, including a trial of 2 concomitant AEDs
- Alabama resident
- Referral packet must be submitted on patient's behalf by primary neurologist
- AEDs, VNS, ketogenic diet all must be stable prior to enrollment
- To date, have enrolled 71 children (49 active) and 66 adults (47 active)
- CBD dosing is weight based, administered twice daily. Dose increased by 5 mg/kg/day to max dose of 50 mg/kg/day

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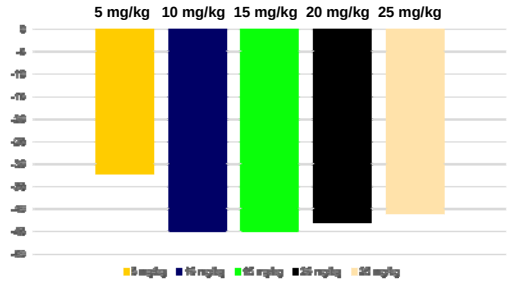
UAB data (N = 51)



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Szaflarski et al., 2016 AES

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Efficacy: UAB Data

- The 3- and 6-month models for all patients were significant (p=0.007 and p=0.002, respectively)
- The most optimal dose of CBD at 3 months ~20mg/kg/day and at 6 months ~25mg/kg/day
- 55/81 (68%) had >25% reduction in seizure frequency,
- 47/81 (58%) had >50% reduction in seizure frequency,
- 29/81 (36%) had >75% reduction in seizure frequency, and
- 7/81 (9%) were seizure free.

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Szaflarski et al., 2016 AES

Seizure Severity: UAB Data

Chalfont Total Score	Change from baseline at 3 months				Change from baseline at 6 months			
	N	Mean Change	SD	p value	N	Mean Change	SD	p value
Adults	29	46.4	50.6	p<0.0001	26	39.3	57.99	p<0.002
Children	28	16.7	21.4	p<0.0003	21	19.4	20.3	p<0.0003
All patients	57	31.8	41.6	p<0.0001	47	30.4	45.9	p<0.0001
All responders	38	*32.6	59.1	**p<0.03	30	*27.1	45.2	**p>0.05
All non-responders	19	*21.9	59.1		17	*18.5	45.2	
Chalfont Seizure Type I Score								
Adults	29	11.7	15.4	p<0.0003	26	10.8	17.0	p<0.0033
Children	28	10.4	16.2	p<0.0022	21	13.5	19.6	p<0.005
All patients	57	11.1	15.7	p<0.0001	47	12.0	18.0	p<0.0001
All responders	37	*31.6	57.2	**p<0.05	29	*25.5	43.7	**p>0.2
All non-responders	19	*22.4	57.2		17	*20.1	43.7	

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DeWolfe et al., 2016 AES

Drug – drug interactions: UAB Data

AED Level Analysis

AED	Adults	Children	Interaction?	p-value
Clobazam/ Desmethylclobazam	12 (137)	15 (66)	Y	< 0.001
Valproate	8 (82)	14 (69)	N	NS
Levetiracetam	9 (92)	11 (54)	N	NS
Phenobarbital	3 (21)	2 (9)	N	NS
Clonazepam	11 (46)	14 (10)	N	NS
Phenytoin	2 (19)	1 (7)	N	NS
Carbamazepine	4 (29)	0	N	NS
Lamotrigine	16 (139)	14 (68)	N	NS
Oxcarbazepine	6 (60)	6 (19)	N	NS
Ethosuximide	0	5 (22)	N	NS
Topiramate	11 (109)	9 (35)	Y	<0.001
Vigabatrin	0	3 (11)	N	NS
Zonisamide	7 (70)	7 (40)	Y (adult)	0.017
Eslicarbazepine	4 (25)	0	Y	0.039
Ezogabine	4 (20)	0	N	NS
Pregabalin	2 (15)	0	N	NS
Perampanel	3 (7)	5 (33)	N	NS
Rufinamide	6 (62)	10 (48)	Y	0.004
Lacosamide	12 (105)	8 (37)	N	NS

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- Interactions were seen between CBD and topiramate, clobazam, and rufinamide in adults and children, and zonisamide and eslicarbazepine in adults.
- Adult subjects reported sedation more frequently with higher N-desmethylclobazam levels (CYP2C19 and CYP2C9 interactions)
- AST and ALT were higher in VPA and CBD (though the average values were still within the normal range)
- CBD also shown to interact with warfarin

Gaston et al., 2017 Epilepsia (in press)
Vipes et al., AES 2016

Dravet study (Phase III RCT)- Devinsky et al., NEJM 2017

Table 3. Summary of Secondary End-Point Results during the Treatment Period (Intention-to-Treat Analysis Set).*

End Point	Cannabidiol vs. Placebo		P Value‖
	Difference (95% CI)	Odds Ratio (95% CI)‡	
Change from baseline in CGIC score	-1.0 (-1.0 to 0.0)§		0.02
Reduction in convulsive seizures from baseline¶			
≥25% reduction		2.10 (1.01 to 4.35)	0.05
≥50% reduction: key secondary end point		2.00 (0.93 to 4.30)	0.08
≥75% reduction		2.21 (0.82 to 5.95)	0.11
100% reduction	4.9 (-0.5 to 10.3)§		0.08
Percentage change from baseline in seizure frequency**			
Total seizures	-19.20 (-39.25 to -1.17)§		0.03
Total nonconvulsive seizures	0.00 (-21.36 to 31.59)§		0.88
Reduction from baseline in duration of seizure subtypes††			
Tonic-clonic seizures		2.48 (0.94 to 6.51)	0.07
Tonic seizures		3.40 (0.52 to 22.23)	0.20
Clonic seizures		1.25 (0.13 to 10.57)	0.84
Atonic seizures		7.44 (0.27 to 204.96)	0.24
Myoclonic seizures		2.89 (0.58 to 14.47)	0.20
Countable partial seizures		6.01 (0.83 to 43.21)	0.08
Other partial seizures		1.00 (<0.01 to >999.99)	1.00
Absence seizures		0.61 (0.14 to 2.62)	0.50
Change from baseline in other variables‡‡			
Sleep-disruption score	-0.4 (-1.5 to 0.7)		0.45
Epworth Sleepiness Scale score	1.5 (-0.2 to 3.2)		0.08
Quality of Life in Childhood Epilepsy score	1.5 (-3.8 to 6.8)		0.58
Vineland-II score	-2.6 (-6.8 to 1.6)		0.21
Inpatient hospitalizations due to epilepsy	0.0 (0.0 to 0.1)		0.54

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Dravet study (Phase III RCT)- Devinsky et al., NEJM 2017

Table 4. Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term.*

System Organ Class and Preferred Term	Cannabidiol (N=61)	Placebo (N=59)
	no. of patients (%)	
Gastrointestinal		
Diarrhea	19 (31)	6 (10)
Vomiting	9 (15)	3 (5)
General		
Fatigue	12 (20)	2 (3)
Pyrexia	9 (15)	5 (8)
Infections: upper respiratory tract infection	7 (11)	5 (8)
Metabolism: decreased appetite	17 (28)	3 (5)
Nervous system		
Convulsion	7 (11)	3 (5)
Lethargy	8 (13)	3 (5)
Somnolence	22 (36)	6 (10)

* Events were classified according to the *Medical Dictionary for Regulatory Activities*, version 17.0.

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LGS study (press release 9/2016)

- Phase III RCT – dose finding study
- 225 patients (76 received CBD at 20 mg/kg/d; 73 CBD at 10 mg/kg/d; 76 placebo)
  - Added to current regimen of 3 AEDs
  - Average age 16 (2-55) years
  - Average number of previously failed AEDs = 7
- Reduction in drop seizures over the treatment period compared to placebo (42% vs. 37% vs. 17%; p=0.001)
- Up to 94% reported mild side effects

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Press release 3/30/2017

- "…GW Pharmaceuticals' cannabinoid Epidiolex has been awarded "orphan status" by European regulators as a treatment for LGS, a rare and severe form of childhood epilepsy.
- Company is preparing application to market the drug in the US for this indication in middle of 2017, followed by a submission to the European Medicines Agency shortly thereafter…"

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Patient Obtained CBD Products/Leni's Law

- In 2016, "Leni's Law" was passed by the AL legislature, legalizing the possession of CBD oil "with a THC content of 3% or less" for the treatment of a "debilitating medical condition" including "those that cause seizures".
- This law does not define the physician/provider's role. Thus, providing no protection to practitioners regarding administration, prescribing/recommending, and dosing.
- However, given the possible drug-drug interactions, appropriate labs should be monitored if a patient begins CBD treatment.

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Conclusions

- Evidence accumulating that CBD is effective and safe anti-convulsant in humans with refractory epilepsy
- Few side effects
- Possible drug interactions with several AEDs
- Epidiolex® likely going for FDA approval in imminent future

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UAB CBD Study

- UAB CBD study is recruiting new participants- visit www.uab.edu/cbd for more information

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