





## 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 <u>under-recognized</u> and <u>under-treated</u>
- New treatments are desperately needed
- Is there a role for Cannabinoids?

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Englot et al., 2012, Neurology













## 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 Theraper Gaston et al., 2017 Epilepsy and Behavior



# 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 Therany)

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Reads day, the self-decays provided





Author (reference)	Number of participants	Age of participants	Diagnosis	Preparation	Dosage	Response
Ames and CridRand [60] Conha et al. [61] Davis and Ramsey [62] GW Pharma [53] Mechoolam and Carlini [54] Porter and Jacobson [65] Trembly and Sherman [66]	12* 15 <sup>9</sup> 5 27 6* 9* 19*	Adults Adults Children Children Adults Children Adults Children Adults	Epilepsy and MR Focal-onset epilepsy Epilepsy Epilepsy Epilepsy Epilepsy and MR Temporal lobe epilepsy Catastrophic epilepsies Epilepsy	CED captules CIID captules THC isomers CIID (Epidiolex) THC CED CED CED,THC	Up to 600 mg/day = 1.5 mg/kg/day Up to 4 mg/day Up to 0.12 mg/kg/day 200 mg/day CBD up to 28 mg/kg/day 100 mg/day	4.8 CBD and 1.8 placebo improv 2.5 improved and 1.5 weekend 13:27 improved 50% or more 4.6 improved 3.4 CBD and 0.5 placebo improv 16/19 improved
• 6	9/102	2 patien	its receiv	ed Ca	nnabis pr	oducts
- 4	2/69	were "r	esponde	rs" (61	%)	
• C	ochr	ane Re	view – "r	io relia	ble concl	usions

	cannabinoids for the treatment of epilepsy" (Gloss
	and Vickerey, 2014)
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Szaflarski & Bebin, 2014 EB

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= 3 3 5 = 8	Surv Star seiz 34%	vey c nford ure c rep	or p wl cor ort	ho ho htro ed	ents usec I (Fa impr	of ch I TH Icebo rover	nildre C/CB Dok) ment:	n tre D pr	ateo odu	d at icts i	for
	• 42%	>80% seizi	ure red	uction							
Patient	Diagnosis	Age and sex	Age at seizure onset	Time on CBD	CBD (mg/kgiday)	THC (mgkgiday)	Seinnes beitre CID	Seizures after CBD	Estimated change in seizure frequency	Number of AEDs tried before CBD	AEDs discontinued while on CBD
Patient	Diegnosis	Age and sex	Age at seizure onset	Time on CBD >1 y	CRD (mg/kg/day) ?	THC (mgkgiday) 7	Seiares bebre CBD >100/day	Seizures after CBD 8-10/day	Estimated change in seizure frequency >=805	Number of ALDs tried before CBD	AEDs decontinued while on CBD Banad, Onfi
Patient	Diagnosis LGS DS	Age and sex 7 y, female 14 y, female	Age at seizure onset	Time on CRD >1 y >4 m	CBD (mg.kg:day) 7 14	THC (mgkgiday) 7 0.5	Seitures beitre CBD >100/day 5/day	Seisures after CIED 8-10/day 0-1/day	Estimated change in seizure frequency >=80%	Number of ALDs tried before CRD 8 12	AEDs discontinued while on CBD Banzel, Onfi
Patient	Diagnosis LGS DS EIMR FS	Age and sex 7 y, female 14 y, female 12 y, female 7 y male	Age at seizure onset	Time on CRD >1 y >4 m 2-4 m	CBD (mg/kgiday) 7 14 7	THC (mgkgiday) 7 05 05 025-05	Seinares bebre CBD > 100/day 5/day 5/day 5/day	Seizums alter CBD 8–10/day 0–1/day 0–1/day Schurock	Estimated change in seizure frequency > - 80% > - 80% 0	Number of AEDs tried before CBD 8 12 17 15	AEDs discontinued while on OED Banzel, Oth
Patient	Diagnosis LGS DS EPMR DS DS	Age and sex 7 y, female 14 y, female 12 y, female 7 y, male 6 y, female	Age at seizure onset <1 y <1 y <1 y <1 y <1 y	Time on CRD >1 y >4 m 2-4 m >4 m >4 m	CBD (mg/kgiday) ? 14 ? 8 4	THC (mgkgiday) 7 05 05 025-05 03-025	Seinares bebre CBD > 100/day 5/day 50/work 200-300/work	Seizums after CBD 8–10/day 0=1/day 0=1/day 5-0/work 0=2/work	Estimated change in seizure frequency > -80% > -80% 0 > -80%	Number of AEDs tried before CBD 8 12 17 16 6	AEDs decontinued while on CBD Bunzel, Onfi
Patient 1 2 3 4 5 6	Diagnosis LCS DS EPMR DS DS DS DS	Age and sex 7 y, female 14 y, female 12 y, female 7 y, male 6 y, female 16 y, female	Age at seizure onset <1 y <1 y <1 y <1 y <1 y <1 y <1 y	Time on CBD >1 y >4 m >4 m >4 m >4 m	(30) (mg/kgiday) 7 14 7 8 4 1-2	THC (mgkgiday) 7 05 05 025-05 01-025 01-025 012-01	Seizures beitere CBD > 100/day 5/day 12/day 50/work 200-300/work 200-300/work	Seinures after CBD 8–10:day 0–1;day 0–1;day 50;tweek 0–2;tweek	Estimated change in seizure frequency >=80% >=80% 0 >=80% -25%	Number of AEDs toled before CBD 8 12 17 16 6 16	AEDs discontinued while on CBD Banzel, Ord Ordf Ordf
Patient 1 2 3 4 5 6 7	Diagnosis Dis DS DS DS DS DS DS DS DS	Age and sex 7 y, female 14 y, female 12 y, female 6 y, female 16 y, female 13 y, male	Age at seizure onset <1 y <1 y <1 y <1 y <1 y <1 y <1 y	Time on CBD >1 y >4 m 2-4 m >4 m >4 m 3-4 m	CBD (mg.kg.iday) 7 14 7 8 4 1-2 4	THC (mgkgiday) 7 0,5 0,5 0,5 0,5 0,2 - 0,5 0,1 - 0,2 5 0,2 - 0,1 0,02 - 0,1	Seinares beitere CBD 5/day 12/day 50/work 200-300/work 200-300/work	Seinues after CBD 8-10/day 0-1/day 0-1/day 50/sweek 0-2/week 4/week 3/doweek	Estimated change in seizure frequency >=80% >=80% 0 >=80% 0 >=80% -25% -25%	Number of ALDs tried before CBD 8 12 17 16 6 16 16 16	AEDs discontinued while on CBD Banati, Ottf Orafi Phonobarbitat, Depakote
Patient 1 2 3 4 5 6 7 8 0	Diagnonia Diagnonia Dis EPMR DIS DIS DIS DIS DIS DIS DIS DIS	Age and sex 7 y, female 14 y, female 2 y, female 6 y, female 16 y, female 13 y, male Male	Age at seisare onset <1 y <1 y <1 y <1 y <1 y <1 y <1 y <1 y	Time on CBD >1 y >4 m >4 m >4 m >4 m >4 m >4 m >4 m	CBD (mg/kgiday) 7 14 7 8 4 1-2 4 5 3-4	THC (mgkgiday) 7 0.5 0.5 0.25-0.5 0.2-0.5 0.2-0.1 0.02-0.1 9 0.04-0.1 9	Seizures beitere CBD 5/day 12/day 20/work 200-300/werek 3/work 3/work 3/work 3/work	Seisues after CBD 8-10/day 0-1/day 0-1/day 50/werk 0-2/werk 30/werk 1-2/werk 1-2/werk	Estimated change in seizure frequency >=80% >=80% 0 >=80% =25% =25% =25% =50%	Number of ALDs tried before CBD 8 12 17 16 6 16 16 16 16 16 16 10	AlDs decenterand while on GED Ranzel, Ord Ordi Ordi Ordi Decelarity Logaliste Elonopis
Patient 1 2 3 4 5 6 7 8 9 10	Diagnosis LGS DS EPMR DS DS DS DS DS DS DS DS DS DS	Age and sex 7 y, female 14 y, female 12 y, female 12 y, female 15 y, female 15 y, female 13 y, male Male	Age at seisare onset <1 y <1 y <1 y <1 y <1 y <1 y <1 y <1 y	Time on CBD >1 y >4 m >4 m >4 m >4 m >4 m >4 m >4 m >4 m	CRD (mg.kg:day) 7 14 7 8 4 1-2 4 3-4 4	THC (mgkgiday) 7 05 025-05 025-05 02-01 02-01 02-01 7 004-02 02-04	Setares before CBD > 100/day 5/64y 12/day 50/work 200-300/work 200-300/work 3/work 3/work 100-500/work 100-500/work	Seisues alter CBD 8-10/day 0-1/day 56/work 0-2/work 4/work 36/work 1-2/work 1-2/work 1-2/work	Estimated change in seizure frequency >80% >80% 0 >80% 25% 25% >50% >80%	Number of AEDs bied before CBD 8 12 17 16 6 16 16 16 16 14 10 12	AIDs discontinued while on CED Banard, Ordf Ordf Ordf Off Phonobal, Depalente STP, Topeman, Depalente STP.
Patient 1 2 3 4 5 6 7 8 9 10 11	Diagnosis Diagnosis DS DS DS DS DS DS DS DS DS DS DS DS DS	Age and sex 7 y, female 14 y, female 12 y, female 6 y, female 15 y, female 13 y, male Male 8 y, female	Age at software onset <1 y <1 y <1 y <1 y <1 y <1 y <1 y <1 y	Time on CID 24 m 24 m 24 m 24 m 34 m 34 m 24 m 24 m 24 m 24 m 24 m 24 m 24 m 2	CBD (mg/kg/day) 7 14 7 8 4 1-2 4 2 3=4 4 2	THC (mgkgiday) 7 05 05 025-05 03-025 022-01 022-01 7 024-02 02-04 7	565.00 kere CBD > 100/day 564.97 12/day 50/work 200-300/work 7/work 40/work 150-500/work 150-500/work 50-500/work 50-500/work	Seitums after CBD 8-10/day 0-1/day 0-1/day 50/sweek 4/week 3/diweek 1-2/week 1-2/week 1-2/week 0-3/week	Estimated change in seiture frequency >=80% >=80% 0 >=80% =25% =50% >=80% >=80% >=80% >=80% >=80%	Number of AIDs mied before CBD 8 12 17 16 6 16 16 16 14 10 12 10	AIDs discontinued while on CBD Banzel, Onfi Ordi Ordi STP, Toppman, Depailote STP, Toppman, Depailote STP, Ordi, Depailote
Patient 1 2 3 4 5 6 7 8 9 10 11 12	Diagnosis Di DS DS DS DS DS DS DS DS DS DS DS DS DS	Age and sex 7 y, female 14 y, female 12 y, female 7 y, male 6 y, female 13 y, male Male 8 y, female 7 y, female 7 y, female	Age at seizure onset <1 y <1 y <1 y <1 y <1 y <1 y <1 y <1 y	Time on CID 2-1 y 2-4 m 2-4 m	CBD (mg.kg:day) 7 14 7 8 4 1-2 4 3-4 3-4 7 3-4 3-4	THC (mgkgiday) 7 0.5 0.5 0.25-0.5 0.22-0.1 0.02-0.1 7 0.04-0.2 0.04-0.2 0.04-0.2	Seitures beitere CBD > 100/day 5/day 12/day 50/work 200-300/work 200-300/work 200-300/work 200-300/work 200-300/work 200-300/work	Seisums after CBD 8-10/day 0-1/day 0-1/day 50/week 0-2/week 4/week 1-2/week 1-2/week 20-50/week 0-3/week 0-3/week 0-3/week	Estimated change in seizer frequency >=80% >=80% 0 >=30% =25% >=30% >=80% >=80% =50%	Number of AEDs used before CBD 8 12 17 16 6 16 16 16 16 16 16 10 10 10 10	AIDs discontinued while on CED Banard, Onff Ordf Ordf Off Phonobal, Depakote SIP, Topoman, Depakote SIP SIP, Ondf, Depakote Onff, Jonegan, Depakote
Patient 1 2 3 4 5 6 7 8 9 10 11 12 13	Diagnosis Diagnosis DS DS DS DS DS DS DS DS DS DS DS DS DS	Age and sex 7 y, femule 14 y, femule 12 y, femule 13 y, male 6 y, femule 13 y, male Male 8 y, femule 7 y, femule 9 y, femule 9 y, femule	Age at seizure onset <1 y <1 y <1 y <1 y <1 y <1 y <1 y <1 y	Time on CID >1 y >4 m >4 m >4 m >4 m >4 m >4 m >4 m >4 m	CRD (mg/kg/day) 7 14 7 8 4 1-2 4 7 3-4 4 7 3-4 10=13	THC (mgkgiday) 7 05 05 025-05 02-01 02-01 7 02-01 7 02-04 7 02-04 7 02-04 7	5einares beitzer CBD >-100/day 50/day 12/day 50/work 200-300/work 3/work 500/work 500/work 500/work 5-10/work 5-10/work 60-250/day	Seisums after CBD 8-10/day 0-1/day 0-1/day 0-1/day 0-1/day 0-1/day 0-2/werk 4/work 0-2/werk 1-2/werk 1-2/werk 0-3/werk 0-10/werk 0-10/werk 0	Estimated change in seizure bropaesky >=80% >=80% 0 >=80% =25% =25% =50% >=80%	Number of AEDs tried before CRD 12 17 16 6 16 16 16 16 16 10 12 10 10 15	AIDs discontinued while on CBD Banzel, Onfi Ordi Ordi STP, Toppana, Depulsore STP, Toppana, Depulsore STP, Onf, Depulsore Ordi, Jonegran, Depulsore Ordi, Jonegran, Depulsore Ordi, Jonegran, Depulsore
Patient 1 2 3 4 5 6 7 8 9 9 10 11 12 13 14	Diagnosis LGS DS EPMR DS DS DS DS DS DS DS DS DS Dcene DS Dcene DS Dcene	Age and sex 7 y, femule 14 y, femule 12 y, femule 6 y, femule 16 y, femule 13 y, mule Male II y, femule 2 y, femule 2 y, mule	Age at setsare onset <1 y <1 y <1 y <1 y <1 y <1 y <1 y <1 y	Time on CID >1 y >4 m >4 m >4 m >4 m >4 m >4 m >4 m >1 y >4 m >4 m >4 m >4 m >4 m >4 m >4 m >4 m	CBD (mg.kg.iday) 7 14 7 8 4 1-2 4 2 3-4 2 3-4 4 7 3-4 10-13 7 7	THC (mgkg:day) 7 05 025-05 022-05 022-01 022-01 022-01 024-02 024-02 024-02 05 005-04 005-04	Seitares beitzer CBD >-100/day 5/day 12/day 200-300/werk 200-300/werk 200-300/werk 200-300/werk 200-300/werk 20-300/werk 20-300/werk 20-300/werk	Seisunes after CBD 8–10./day 0–1./day 56/week 0–2./week 36/week 1–2./week 20–56/week 0–3./week 0–3./week 0–10./week 0–10./week 0–0./week	Estimated change in seizure ferquency > -80% > -80% 0 > -80% -25% > -80% -80% -60% -60% > -80% > -80%	Number of AED utied before CBD 12 17 16 6 16 16 16 16 14 10 10 10 15 4 2 2 2 2 2 2 2 2 2 2 2 2 2	AID's discentioned while on CRD Banard, Ortf Ordf Ordf Silonopia SIP, Topennas, Depulate SIP SIP, Ond, Depulate SIP SIP, Ond, Depulate Lossarpam, ethoracimide
Patient 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	Diagnosis Dis Dis Dis Dis Dis Dis Dis Dis Dis	Age and sex 7 y, female 14 y, female 12 y, female 13 y, female 16 y, female 16 y, female 13 y, male Male 8 y, female 2 y, female 2 y, female 2 y, female 10 y, fe	Age at seizure onset <1 y <1 y <1 y <1 y <1 y <1 y <1 y <1 y	Time on CED >1 y >4 m >4 m >4 m >4 m >4 m >4 m >4 m >4 m	CBD (mg/kgiday) 7 14 7 8 4 1-2 4 7 3-4 4 7 3-4 10-13 7 7 v055 6	THC (mgkgday) 7 05 05 025-05 02-05 02-01 7 02-01 7 02-04 7 7 04-02 05 004-02 05 004-02 05 004-02 05-05	Seinares beitker CBD > 100/day 5/iday 12/day 50/work 200-300/work 7/work 200-300/work 50-10/work 200-300/work 5-10/work 200-300/work	Seisums after CBD 8-10/day 0-1/day 0-1/day 50/werk 4/work 30/werk 1-2/werk 1-2/werk 1-2/werk 0-3/werk 0-10/werk 0-10/werk 0-10/werk 4/work 0-1/werk 0-1/werk 0-1/werk 1-2/werk 0-1/werk 0-1/werk 1-2/werk 1-2/werk 0-1/werk 1-2/werk 0-1/werk 0-1/werk 0-1/werk 1-2/werk 0-1/werk 0-	Estimated change in before frequency >=005 >=305 0 ==255 ==255 >=305 >=305 >=305 ==305 ==305 0 0 ===505	Number of ALDs thed before CBD	AID's discentioned while on CRD Banati, Onfi Oodi Ordi, Phonohethal, Depakote SD: Toppman, Depakote Ordi, Zanggan, Depakote Ordi, Zanggan, Depakote Ordi, Zanggan, Depakote
Patient 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 17	Diagnosis LCS DS DS DS DS DS DS DS DS DS DS DS DS Doore Doore	Age and sex 7 y, female 14 y, female 12 y, female 6 y, female 13 y, male Male 8 y, female 2 y, female 2 y, female 13 y, male 14 y, female 13 y, male 11 y, male	Age at seizure onset <1 y <1 y 2-5 y 2-5 y	Time on CBD 2-1 y 2-4 m 2-4 m	CBD (mg/kgiday) 7 14 7 8 4 1-2 4 7 3-4 4 7 3-4 10-13 7 ~0.5 6 6	THC (mgkgide) 05 025-03 022-03 022-01 7 024-02 02-04 7 024-02 05 04-02 05 04-02 05 04-03 06-08 0	Seitures before CBD before CBD 5.04ay 5.04ay 5.04ary 5.04ary 5.04aresk 2.00-3.00/week 2.00-3.00/week 2.00-3.00/week 2.0-3.00/week 2.0-3.00/week 2.0-3.00/week 2.0-3.00/week 2.0-3.00/week 2.0-3.00/week 2.0-3.00/week 2.0-3.00/week 2.0-3.00/week 2.0-3.00/week	Seinurs after CRD 8-10.day 0=1.day 0=1.day 0=2.week 4.vaeck 1=2.week 1=2.week 0=10.week 0=10.week 0=10.week 0=10.week 0=10.week 0=10.week 0=10.week 0=0.0000000000000000000000000000000000	Estimated charge in seizure >=30% >=30% >=30% =25% =25% =30% >=30% >=30% >=30% >=30% >=30% >=30% >=30% >=30% >=30% >=30% >=30% >=30%	Number of AIDs thed before CBD # 12 17 16 6 16 16 16 16 16 16 16 16 16 16 16 1	AIDs discontisued while on CID Banet, Ont Out Out Out Strapping STP: Expense, Depaker STP: STP: STP: Opena, Depaker STP: STP: Opena, Depaker STP: STP: Opena, Depaker STP: STP: Opena, Depaker STP: STP: Opena, Stp. Strapping StP: StP: StP: StP: StP: StP: StP: StP:
Patient 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	Diagnesis Diagnesis Dis Dis Dis Dis Dis Dis Dis Dis Dis	Age and sex 7 y, female 14 y, female 12 y, female 12 y, female 13 y, enale 13 y, male Male 8 y, female 2 y, male 11 y, male Female	Age at setsure onset <1 y <1 y <1 y <1 y <1 y <1 y <1 y <1 y	Time on CBD >1 y >4 m >4 m >4 m >4 m >4 m >4 m >4 m >4 m	CBD (mg/kg:idy) 7 14 7 8 4 1-2 4 7 3-4 4 7 3-4 4 7 3-4 9 3-4 6 6 6 6 6 28	THC (mgkgdq/) 7 05 025-035 022-03 022-03 022-03 022-01 022-01 022-04 7 024-02 028-04 028-04 028-04 028-04 008-04 008-05 0 05-05 0 05-05	Solitares bekere CBD >100/day 5/day 12/day 200-300/wwek 3/work 200-300/wwek 3/work 200-300/wwek 200-300/wwek 200-300/wwek 200-300/wwek 200-300/wwek 200-300/wwek 200-300/day 12/work 15-20/day 13/wwek	Seisues after CBD 0=1,64y 0=1,64y 0=1,64y 5-0,work 1=2,work 1=2,work 1=2,work 0=3,work 0=1,0,work 0=1,0,work 0=1,0,work 0=1,0,work 0=1,0,work 0=1,0,work 0=1,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,	Estimated charge in seizure frequency >=80% >=80% >=80% >=80% >=80% >=80% >=80% >=80% >=80% >=80% >=80% >=80% >=80% >=80%	Number of AEDs thed before CRD # 12 17 16 6 16 16 16 16 16 16 16 16	AIDs decentioned while on CED Banat, Ortf Oost Oost Phonolating (hypolase Congress) STP, Ont, Dagalane Congress, Dagalane Congr



### **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</li>

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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





### Efficacy: UAB Data

Szaflarski et al., 2016 AES

- The 3- and 6-month models for all patients were significant (p=0.007 and p=0.002, respectively)
- <u>The most optimal dose of CBD at 3 months ~20mg/kg/day and at 6 months ~25mg/kg/day</u>
- 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.

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<0.00	
Children	28	16.7	21.4	p<0.0003	21	19.4	20.3	p<0.000	
All patients	57	31.8	41.6	p<0.0001	47	30.4	45.9	p<0.000	
All responders	38	*32.6	59.1	******** 0.03	30	*27.1	45.2	****>0 (	
All non-responders	19	*21.9	59.1	p~0.00	17	*18.5	45.2	p=0.0	
Chalfont									
Seizure Type I									
Score									
Adults	29	11.7	15.4	p<0.0003	26	10.8	17.0	p<0.00	
Children	28	10.4	16.2	p<0.0022	21	13.5	19.6	p<0.00	
All patients	57	11.1	15.7	p<0.0001	47	12.0	18.0	p<0.00	
All responders	37	*31.6	57.2	**n<0.05	29	*25.5	43.7	**n>0	
All non-responders	19	*22.4	57.2	p -0.00	17	*20.1	43.7	p=0.	

			Drug	– drug	interactions: UAB Data
AED Level Analysis					r
					<ul> <li>Interactions were seen</li> </ul>
AED	Adults	Ovlideen	Interaction?	puste	
Clobazam/ Desmethylclobazam	12 (137)	15 (66)	Y	< 0.001	clobazam, and rufinamide in
Valproate	8 (82)	14 (69)	N	NS	adulta and shildron, and
Levelizacetam	9 (92)	11 (54)	N	NS	adults and children, and
Phenobarbital	3 (21)	2 (9)	N	NS	zonisamide and eslicarbazepine ir
Clonazepam	11 (46)	14 (10)	N	NS	adults
Phenytoin	2 (29)	1 (7)	N	NS	
Carbamazepine	4 (29)	0	N	NS	<ul> <li>Adult subjects reported</li> </ul>
Lamotrigine	16 (139)	24 (68)	N	NS	sedation more frequently with
Oxerbarepiere	6 (60)	6 (19)	N	N5	higher N-desmethylclobazam
Ethouaimide	0	5 (22)	N	NS	
Topiramate	11 (109)	9 (35)	¥	+0.001	levels (CYP2C19 and CYP2C9
Vigabatrin	0	3 (11)	N	N5	interactions)
Zonisamide	7 (70)	7 (40)	Y (adult)	0.017	AST and ALT wore higher in
Eslicarbacepine	4 (25)	0	¥	0.039	AST and ALT were higher in
Egozabine	4 (20)	0	N	NS	VPA and CBD (though the
Pregabalin	2 (15)	0	N	NS	average values were still within
Pesampanel	3 (7)	5 (33)	N	NS	the normal range)
Rufinamide	\$ (62)	10 (48)	Y	0.004	(ne normananye)
Lacosamide	12 (103)	# (37)	N	85	<ul> <li>CBD also shown to interact</li> </ul>
UB	MED	KANE			with warfarin
tion in the second second	ter all de	age year and b			Gaston et al., 2017 Epilepsia (in press) Vines et al., AES 2016







Table 4. Adverse Events Occurring Either Trial Group, According to System	Table 4. Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term. <sup>4</sup>							
System Organ Class and Preferred Term	System Organ Class Cannabidiol Placebo and Preferred Term (N = 61) (N = 59) no. of patients (%)							
Gastrointestinal	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)						



## 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

### 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..."

## 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 <u>does not</u> define the physician/provider's role. Thus, <u>providing no protection</u> 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.

### 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 participantsvisit <u>www.uab.edu/cbd</u> for more information