Cannabinoids for the treatment of epilepsy

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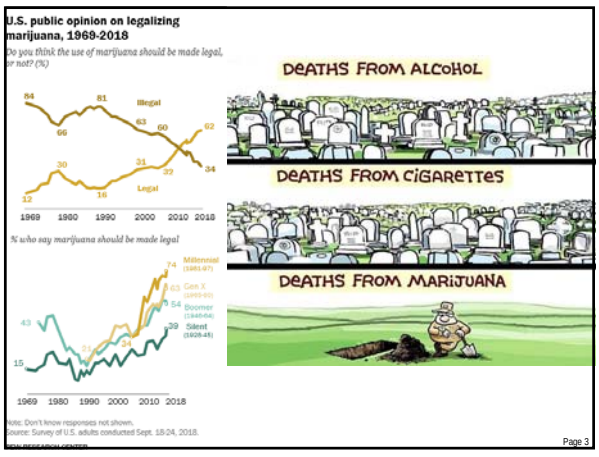
Knowledge that will change your world



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Definitions (NIDA)

- *Cannabinoids*
  - Chemicals derived from the Cannabis plant (or manufactured)
  - Dronabinol (pill and liquid) and Nabilone – synthetic FDA-approved Δ-9 THC/ Δ-9 THC-like products
- *Medical cannabis (medical marijuana; MMJ)*
  - Whole, unprocessed cannabis plant or its basic extracts to treat symptoms of illness and other conditions
  - FDA has not recognized or approved the cannabis plant as medicine
  - MMJ (marijuana/marihuana) – in the US this term is somewhat pejorative as it was first used by law enforcement to demonize the use of MMJ by immigrants ("something used by others")
- "Because the [cannabis] plant contains chemicals that *may* help treat a range of illnesses and symptoms, many people argue that it *should* be legal for *medicinal* purposes…"

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Anthony et al., 2017 Curr Pharm Des; Mead 2017 EB

Pacher and Kunos, FEBS Journal 2013

"…Modulating the endocannabinoid system (ECS) holds therapeutic potential in a broad range of diseases affecting humans…"

"… modulating endocannabinoid activity may have therapeutic potential in almost all disease affecting humans including obesity/metabolic syndrome, diabetes and diabetic complications, neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal, skin diseases, pain, psychiatric disorders, cachexia, cancer, chemotherapy-induced nausea and vomiting, among many others… (p. 1918)

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Endocannabinoid System

- Group of receptors and lipid neurotransmitters involved in physiological processes:
  - Appetite, pain/sensation, mood, memory, immune function, female reproduction, sleep…
  - "Mediation of psychoactive effects of cannabis"
- Cannabinoid receptors: CB_1 and CB_2
  - CB_1 – "central" and CB_2 – "peripheral" (mainly located on blood cells and in immune tissue)
  - G-protein-coupled (or other mechanisms)
- Endocannabinoids:
  - "Endocannabinoid tone"
  - Anandamide (AEA)
  - 2-arachidonoylglycerol (2-AG)
  - "On demand" synthesis potentially in response to elevated intracellular Ca^{++}
  - Once released inactivated by glia
    - AEA – FAAH or NAAA or COX-2
    - 2AG – MAGL or COX-2 (lesser degree ABHD6, ABHD12 and FAAH)

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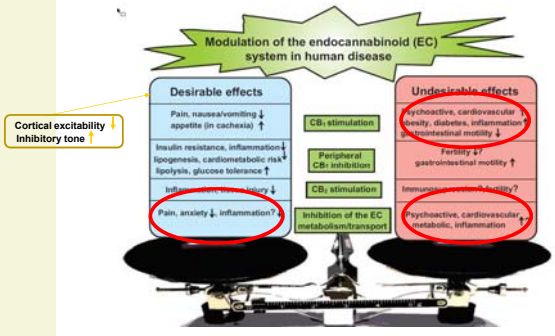
ECS: "Relax, eat, sleep, forget, and protect"



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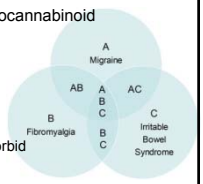
Modified after Ethan Russo, MD

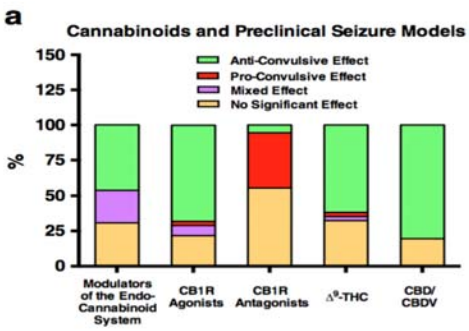
Ethan Russo, MD

- Clinical Endocannabinoid Deficiency (CED)
  - All humans possess underlying "endocannabinoid tone" that reflects the levels of AEA and 2-AG
  - Brain disorders are associated with endocannabinoid neurotransmitter deficiency(ies)
  - CED manifests as a
    - Hyperalgesic state
    - Elevated anxiety/depression
    - They (FBM, migraine, and IBS) are comorbid
  - Diagnoses of exclusion
  - Theory expanded to include many unexplained conditions e.g., neonatal failure to thrive, causalgia, phantom limb pain, etc.



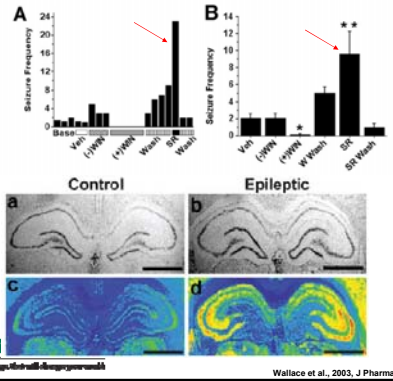
Russo 2016 Cannabis and Cannabinoid Research

Cannabinoids in epilepsy: experimental evidence



Rosenberg et al., Neurotherapeutics 2015
Rosenberg et al., Epilepsy and Behavior 2017

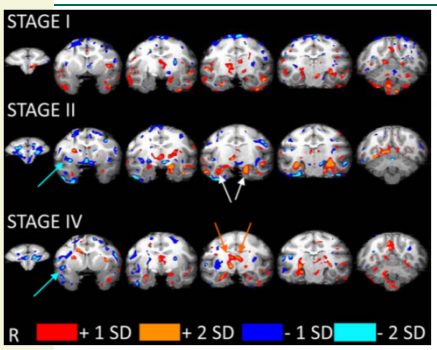
ECS and its role in epilepsy



- Seizure increase with SR141716A (CB_1R antagonist) suggests that cannabinoids decrease hyperexcitability
- Increased CB_1R indicates compensatory mechanism of seizure manifestation

Wallace et al., 2003, J Pharmacology and Exp Therapeutics

Cleeren et al., Epilepsia (2018)



- 2 rhesus monkeys
- TLE model (electrical amygdala kindling)
- [18F]-MK-9470 (CB_1R)
- Red – increase in CB_1R binding

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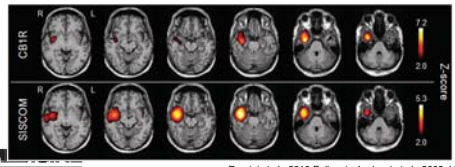
Human data

- New onset TLE – patients had lower levels of CSF AEA compared to HCs
- Patients undergoing ATL had lower CB_1-RNA for DAGL-alpha compared to non-epilepsy controls (less "on demand" production of 2-AG)
- PET – Increased availability of CB_1 receptor in TL compared to HCs ([18F]-MK-9470 (CB_1R))



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Romigi et al., 2010 Epilepsia; Ludanyi et al., 2008 J Neurosc; Goffin et al., 2011 Brain

Overall MOA CBD and Δ-9 THC

- Δ-9 THC
  - CB_1R and CB_2R
- CBD
  - Transient receptor potential (TRP) of vanilloid type-1 (TPRV1)
  - G-protein coupled receptor (GPR55)
  - A_1R and A_2R
  - ECS modulation (allosteric CB_1R and CB_2R)

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- Tested: marijuana, sinsemilla (proportion of sinsemilla to marijuana is increasing), kilobrick, Thai stacks, hashish, hash oil, and ditchweed
- THC:CBD ratio has increased from 14:1 in 2001 to 80:1 in 2014

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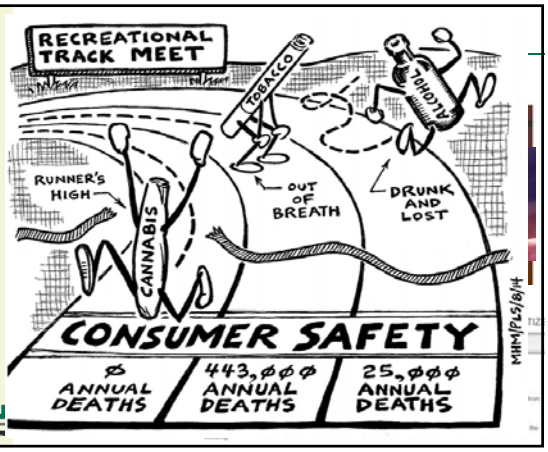
ElSohly et al., 2016 Biological Psychiatry



Cannabis Withdrawal

- Abrupt withdrawal may cause:
  - Jitteriness/irritability
  - Anorexia, cravings, and GI upset
  - Anxiety
  - Insomnia
- Testing for use:
  - Plasma half-life is ~56 hours in occasional users and ~28 hours in chronic users
  - THC can be tested in blood, urine, hair, saliva or sweat
  - Concentration obtained via HPLC techniques can be helpful in distinguishing passive exposure and active use
  - Screening for use via Duquenois-Levine test – sensitive but not very specific (many false positives and e.g., zinc supplements can mask the presence of THC); HPLC is a confirmatory test

Epigenetic effects

- Epigenetic – modulating gene expression without altering the genetic code
- DNA methylation
- Histone modifications
- Noncoding RNAs (gene expression regulation at a transcriptional and post-transcriptional level)
- Sperm epigenome (DNA methylation) different between Cannabis users (active vs. abstinent) and non-users

NCT03614637 (clinicaltrials.gov)
Szutorisz & Hurd 2016 Biol Psychiatry

Youth and Cannabis

- Results from this 2016 Barometer indicate that states such as Utah (4.5%), Alabama (5.2%), and Iowa (5.3%) had the lowest percentage of past-month marijuana use among youth aged 12-17 compared to the corresponding national annual average of 7.2%.
- However, states such as Colorado (11.1%), Vermont (10.9%), and Alaska (10.6%) had the highest percentage of past-month marijuana use among youth.

https://www.samhsa.gov/newsroom/press-announcements/201708101100

Children and Adolescents

- In animal models exposure to THC or analogues (WIN or CP-55):
  - Alterations in maturation of the ECS and dysregulation of neurotransmitter systems maturation (GABA and glutamate)
    - May predispose to psychotic-like symptoms in adulthood
  - Long-term impairment in learning and memory
  - Effect on anxiety is unclear
  - Negative effect on social behavior and emergence of depression-like signs
  - End-product: picture resembling the one present in schizophrenia patients (schizophrenia-like symptoms)

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Rubino et al., 2016 Biological Psychiatry

Children and Adolescents

- Short-term use
  - Impairment of memory and judgement
  - Decreased coordination (i.e., accidents)
  - Paranoia and psychosis
- Long-term and heavy use
  - "Gateway drug": 17% of adolescent users develop addiction to other drugs
  - Cognitive impairment including loss of IQ points
    - Diminished lifetime satisfaction and achievement
  - Increased risk of anxiety and depression
  - Increased risk of psychosis and schizophrenia-like symptoms in persons with predisposition

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Volkow et al., 2014 NEJM

Neurologic complications of Cannabis

- Cognition and behavior
  - Controversial in adults but there is mounting evidence that marijuana use in children and adolescents damages the brain.
  - In-utero exposure can cause long-lasting executive dysfunction
- Stroke
  - 98 (13 synthetic e.g., spice or K2) marijuana-related strokes reported with 5x higher incidence in men; there were 9 hemorrhagic and 5 undetermined strokes
  - Only one study suggested the relationship may be coincidental b/o prevalence of marijuana use
  - Vascular events within 30-60 minutes of marijuana use are likely not coincidental
  - Mechanism: likely reversible cerebral angiopathy (or vasoconstriction syndrome; RCVS)
    - RCVS – thunderclap HA with or without other neurological symptoms, resolves gradually over 1-3 months
- Seizures

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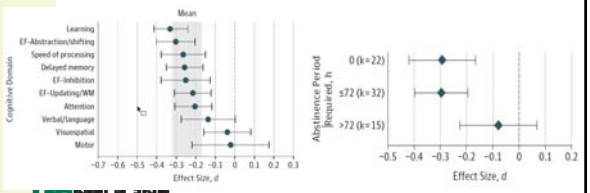
Overall: Effects of Cannabis on Cognition

- Meta-analysis: 2152 cannabis users / 6575 comparison subjects
- Overall, the effect on cognition is small (*d* = -0.25; CI -0.32 to -0.17)
- If abstinent ≥72 hours the effect on is not significant (*d* = -0.08; CI -0.22 to 0.07)
- Abstinence for ≥ 72 hours diminishes the cognitive effects of cannabis use
- "Effects on cognition are relatively small and may be of questionable clinical importance"



Scott et al., 2018 JAMA Psychiatry

CBD vs. THC

- Effects on mood are divergent (2008)
  - Hair samples of 54 individuals who screened (+) for cannabis
  - 3 groups THC only; THC+CBD; negative hair testing
  - THC only showed higher schizophrenia-like symptoms than THC+CBD or negative group
- Effects on memory are divergent (2010)
  - 134 cannabis smokers (own supply)
  - THC:CBD content measured in own supply and saliva
  - Independent of THC content, high CBD content was associated with no memory impairment

Morgan et al, 2008, 2010 B J Psychiatry

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Anti-seizure drugs (ASDs)

- ???? – cannabis
- 1857 – bromides
- 1912 – phenobarbital (PB)
- 1937 – phenytoin (PHT)
- 1944 – trimethadione
- 1954 – primidone
- 1958 – ACTH
- 1960 – ethosuximide (ESM)
- 1963 – diazepam
- 1974 – carbamazepine (CBZ)
- 1975 – clonazepam (CZP)
- 1978 – valproate (VPA)
- 1993 – felbamate (FBM), gabapentin (GBP)
- 1995 – lamotrigine (LTG)
- 1997 – topiramate (TPM), tiagabine (TGB)
- 1999 – levetiracetam (LEV)
- 2000 – oxcarbazepine (OXC), zonisamide (ZNS)
- 2005 – pregabalin (PGB)
- 2008 – lacosamide (LCM), rufinamide (RUF)
- 2009 – vigabatrin (VGB)
- 2011 – retigabine
- 2012 – clobazam (CLB), perampanel (PER)
- 2013 – eslicarbazepine (ESL)
- 2016 – brivaracetam (BRV)
- 2018 – cannabidiol (CBD)

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Drug Development: Industry vs. MMJ

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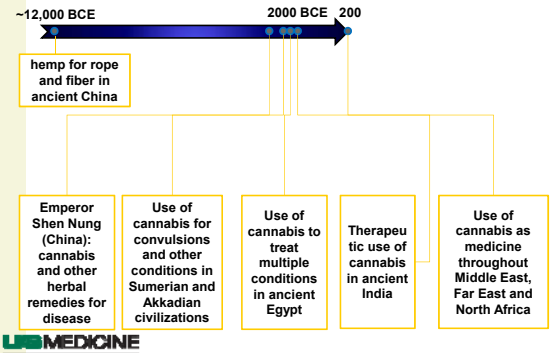
Early history



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1200 1800 1900 1990

cannabis for seizures by Islamic physicians

1619 King James I ordered colonists in America grow 100 hemp plants

1842: O'Shaughnessy promotes cannabis for treatment of numerous conditions including seizures

1881: Gowers describes use of cannabis for epilepsy

Discovery of cannabinoid receptor and endo-cannabinoid signaling system

Synthesis of CBD and Δ9-THC

Human trials of MMJ and CBD for epilepsy

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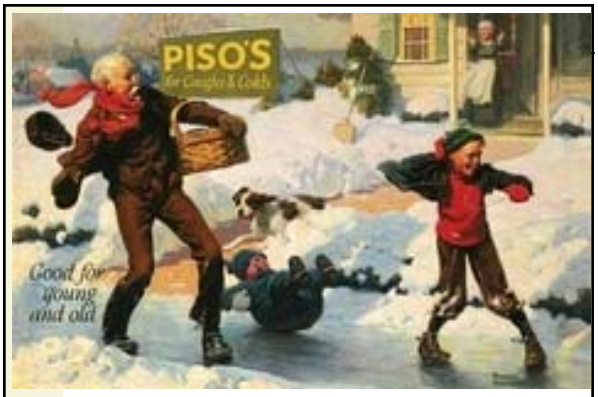

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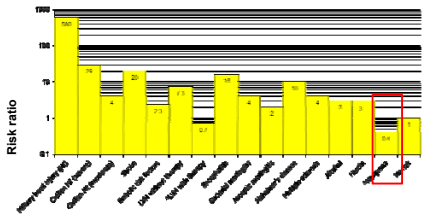
Risk Factors for Epilepsy



LVH = left ventricular hypertrophy.
*Protective.

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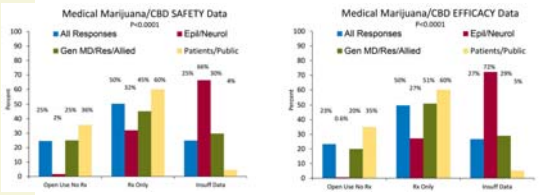
Hesdorffer DC, Verity CM. In: Engel J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*; vol 1. Philadelphia, Pa: Lippincott-Raven Publishers; 1997:59-67.

Opinion: Safety of Cannabis in Epilepsy



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Mathern et al., 2015 Epilepsia

Summary of efficacy data prior to 2015

Author (reference)	Number of participants	Age of participants	Diagnosis	Preparation	Dosage	Response
Ames and Cridland [60]	12[a]	Adults	Epilepsy and MR	CBD capsules	Up to 600 mg/day	–
Cunha et al. [61]	15[b]	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[c]	Children	Epilepsy and MR	THC	Up to 0.12 mg/kg/day	4/6 improved
Mechoulam and Carlini [64]	9[d]	Adults	Temporal lobe epilepsy	CBD	200 mg/day	3/4 CBD and 0/5 placebo improved
Porter and Jacobson [65]	19[e]	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[f]	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”

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Szaflarski & Bebin, 2014 EB;
Gloss and Vickrey, 2014 Cochrane Review

A case for a pharmaceutical grade product

- Dispensaries in San Francisco, Los Angeles, Seattle (randomly selected)
- 75 edible products of different brands
- 17% labelling of content was accurate
  - 23% under-labelled
  - 60% over-labelled
- For non-THC content:
  - 17% were labelled as (+)
  - 59% had non-THC content

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Vandrey et al., 2015 JAMA

A case for a pharmaceutical grade product

	Cannabidiol Extract Products			
	Oil (n = 40)	Tincture (n = 20)	Vaporization Liquid (n = 24)	Total (N = 84)
Label accuracy, No. of products (%) [95% CI]				
Accurate[a]	18 (45.00) [30.71-60.17]	5 (25.00) [11.19-46.87]		
Under[b]	10 (25.00) [14.19-40.19]	8 (40.00) [21.88-61.34]		
Over[c]	12 (30.00) [18.07-45.43]	7 (35.00) [18.12-56.71]		
Labeled concentration, mg/mL				
Mean (95% CI)	56.15 (14.23-98.07)	11.14 (5.60-16.60)		
Median (range)	22.26 (2.50-800.00)	8.33 (1.33-50.00)		
Deviation of labeled content from tested value, mg/mL				
Mean (95% CI) [% of deviation]	10.34 (4.95-15.74) [29.01]	3.94 (2.74-5.14) [220.62]	[illegible]	[illegible]
Median (range) [% of deviation]	2.76 (0.13-144.73) [12.11]	1.48 (0.01-22.30) [19.12]	4.62 (0.14-66.07) [67.34]	3.17 (0.10-144.73) [20.42]

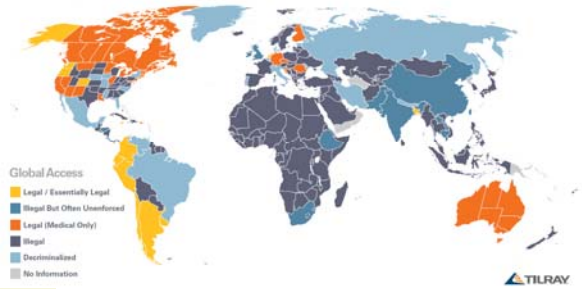
Bon-Miller et al., 2017 JAMA

Perspective

- US: 3.4M people have epilepsy (1.2%)
  - ~1M are medically intractable despite best medical and surgical treatment
- ~Worldwide, ~70M people have epilepsy
  - 20-30M medically intractable
- Intractable epilepsy is under-recognized and under-treated
- Efficacious treatments are needed
  - Is there a role for *Cannabinoids*?

Englot et al., 2012, Neurology; CDC 2017

Available Medical Cannabis Products



Krawczynski et al., 2017 Standarty Medyczne

Artisanal Cannabis Products

Reference	Number of Participants	Age of Participants	Diagnosis	Preparation	Dosage	Response
Artisanal (various or not tested ratios of CBD:THC)						
Sulak et al [27]	272	Adults and Children	TRE, LGS, Dravet Syndrome, Rett Syndrome	Varied	Varied	61% reduction in seizures
Press et al [28]	75	Children and Adolescents	TRE	"Oral Cannabis Extracts"	Varied	57% reported improvement in seizure frequency
Hussain et al [30]	117	Children	TRE, LGS, Epileptic Spasms	Unknown, if reported 15:1 CBD:THC	Median dose 4.3 mg/kg/day	85% reported improvement in seizure frequency; survey
Tzadok et al [31]	74	Children	TRE	20:1 CBD:THC	1-20 mg/kg/day	Significant decrease in seizures in 89% of participants
Hausman-Kedem et al [32]	46	Adults and Children	TRE	20:1 CBD:THC	11.4 mg/kg/day (average dose)	80% reduction in patients taking >11 mg/kg/day, 50% reduction <11 mg/kg/day
Suraev et al [33]	976	Adults and Children	TRE	Varied	Varied	90% adults and 71% children reported seizure improvement]; survey
Suraev et al [34]	41	Children	Mostly TRE	Varied	Varied	38/51 products were considered efficacious by the users; survey

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Gaston and Szaflarski., 2018 CNNR

Treatment duration and expectation of efficacy

- Artisanal Oral Cannabis Extracts (OCEs)
- Press et al.
  - 75 children (57% improvement; 33% responders)
  - RR 22% "locals" vs. 47% "transplants"
- Treat et al.
  - Of 119 children 71% terminated use
  - Average treatment duration – 11.7 months (0.3-57)
  - Relocation to CO associated with perceived benefit (65% vs. 38%; p=0.01)
- Espay et al.
  - FMRI PD study
  - Expectation of efficacy was associated with 28% improvement (not different from levodopa response)

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Press et al., 2015 EB; Treat et al., 2016 Epilepsia; Espay et al., 2015 Neurology

Open-label studies of highly-purified CBD (Epidiolex®)

Reference	Number of Participants	Age of Participants	Diagnosis	Preparation	Dosage	Response
Open Label Studies of Pharmaceutical Grade Cannabidiol (Epidiolex®)						
Devinsky et al [36]	162	Adults and children	TRE	Highly purified CBD oral solution	2-50 mg/kg/day	34.6% median seizure reduction
Szaflarski et al [37]	580	Adults and children	TRE	Highly purified CBD oral solution	2-50 mg/kg/day	48% total seizure reduction
Szaflarski et al [38]	132	Adults and children	TRE	Highly purified CBD oral solution	5-50 mg/kg/day	63.6.% mean seizure reduction at 12 weeks
Hess et at [39]	18	Adults and children	Tuberous Sclerosis	Highly purified CBD oral solution	5-50 mg/kg/day	48.8% median seizure reduction at 12 weeks
Devinsky et al [40]	55	Adults and children	Epileptic Encephalopathies	Highly purified CBD oral solution	5-50 mg/kg/day	51.4% mean seizure reduction at 12 weeks
Gofshteyn et al [41]	7	Children	FIRES	Highly purified CBD oral solution	5-25 mg/kg/day	6/7 had improved seizure frequency

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Gaston and Szaflarski., 2018 CNNR

"CBD products"

- Porcari et al., 2018 (Tennessee)
  - "CBD-containing product"
  - 39% >50% improvement (N=133)
  - No difference between patients on CBD vs. CBD+CLB
- Pietrafusa et al., 2019 (Italy)
  - Crystalline CBD (98-99%)
  - 37% >50% improvement (N=29)
  - No difference between patients on CBD vs. CBD+CLB

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McCoy et al., 2018

- Pharmaceutical grade CBD:THC (50:1)
- Tilray (The Little Rocky Project)
- 20 patients with DS
- Dose
  - CBD 2 to 16 mg/kg/day
  - THC 0.04 to 0.32 mg/kg/day
- 19/20 completed
- Improved QOL, EEG biomarker, motor seizure frequency (70.6%) with 50% RR of 63%

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RCT – Dravet Syndrome

- First CBT Phase III RCT reported
- 120 patients (61 received CBD at 20 mg/kg/d vs. 60 PCBO)
  - Added to current regimen of up to 3 AEDs
  - Average age 9.8 ± 4.8 years
  - Average number of previously failed AEDs = 4.6 ± 3.8 and concurrent 2.9 ± 1.0
- Reduction in convulsive seizures over the treatment period compared to placebo
  - Baseline 12.4 vs. 14.9
  - Treatment period 5.9 vs. 14.1
  - Percentage change p=0.01
- 84% reported mild side effects

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Devinsky et al., 2017 NEJM

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 (0.15 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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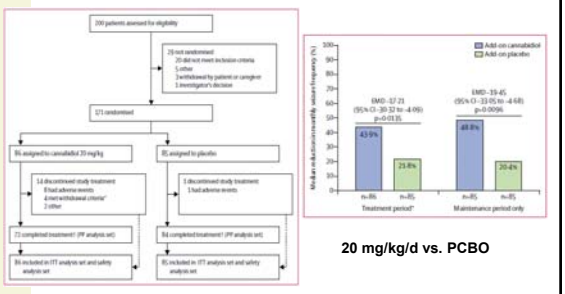
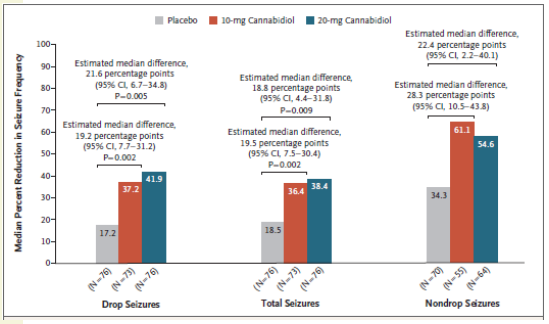
RCT - LGS



20 mg/kg/d vs. PCBO

Thiele et al., 2018 Lancet Neurology

RCT - LGS



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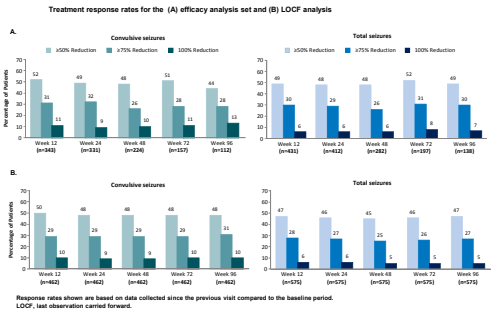
Sustained treatment response



Response rates shown are based on data collected since the previous visit compared to the baseline period.
LOCF, last observation carried forward.

Szaflarski et al., 2018 Epilepsia

Is response related to interactions?

- Dravet Syndrome RCT (Devinsky et al. NEJM 2017)
  - 65% received Clobazam
  - 42% received Stiripentol
  - Both raise nCLB level; Stiripentol also CLB levels
  - Both inhibit CYP2C19
  - CBD results in 1.7-2.6 fold increase
- But, in subsequent letter they avoid addressing whether there were differences

Word of caution

- CBDV IV trial (Greenwich Pharmaceuticals) – not efficacious – phase I
- Synthetic CBD patch (Zynerba, Inc) – phase III not efficacious
  - STAR I
  - STAR II
- Synthetic CBD (INSYS Therapeutics) – phase I only (interactions results only)

Is the response related to interactions?

- UAB data 114/132 at 12 weeks
  - 45 on Clobazam (24 adults/21 children)
  - No significant difference in
    - Seizure reduction (% frequency or absolute reduction)
    - Seizure severity (Chalfont) was different between groups (regression p=0.03) but paired samples T-test was not significant
  - Overall conclusion: Concomitant Clobazam has no effect on seizure frequency

UAB MEDICINE

Gaston et al., 2019 Epilepsy and Behavior

Drug – drug interactions: UAB Data

- CBD T1/2 ~24 hours
- 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)

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
Egozabine	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 (103)	8 (37)	N	NS

UAB MEDICINE

Gaston et al., 2017 Epilepsia

Summary (Epilepsy)

- CBD has clear efficacy in the treatment of epilepsy
- Effect is likely multifactorial and includes modulation of the ECS
- Efficacy of THC or THC/CBD combinations is still unclear
- Stay tuned….

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