Medical Cannabis for Children

Bonni S. Goldstein, MD
Medical Director
Canna-Centers Wellness & Education

MUSC 2nd Annual Update on Medical Cannabis
September 27, 2019

Bonni S. Goldstein, MD

CA Licensed 28 years

Trained at Childrens Hospital Los Angeles (CHLA)

Chief Resident CHLA

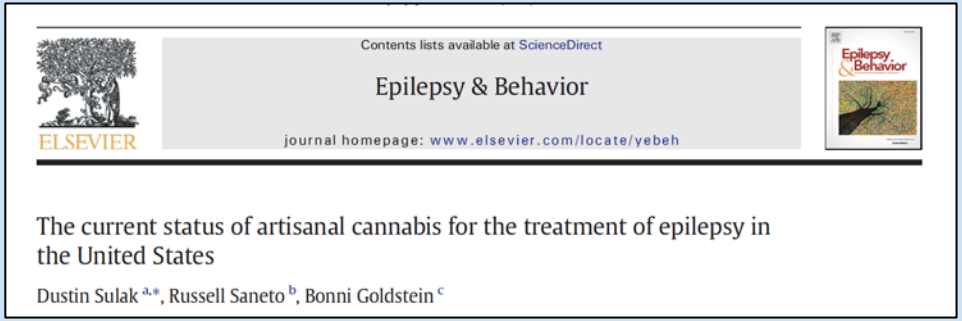
Critical Care Transport Physician

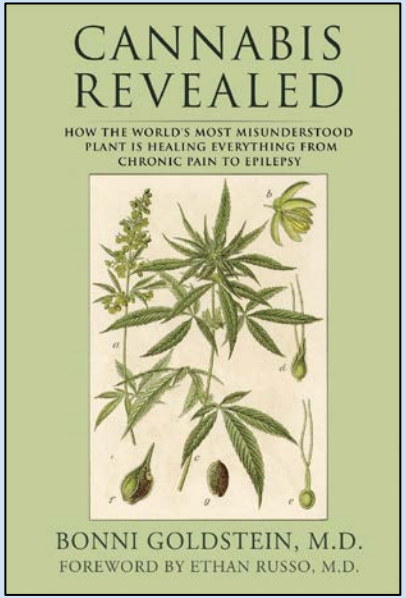
Pediatric Emergency Medicine LA County/USC

Medical Director of Canna-Centers since 2008

Over 10,000 patients treated including ~900 children

No conflicts to report





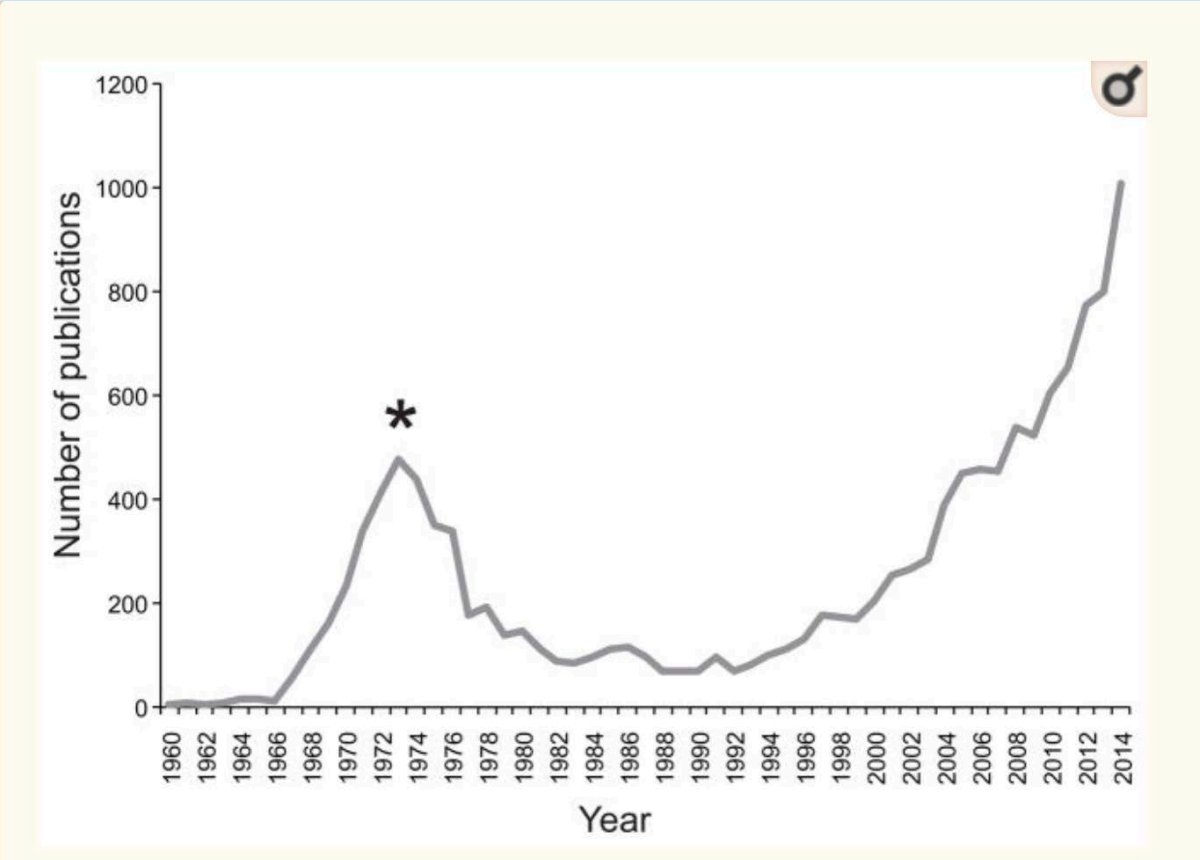
Opened in 2008 in Los Angeles

- **~ 250 patient visits per month**
- **~ 50+ new patient inquiries per month**
- **Youngest patient 6 weeks, oldest 100 years**
- **~ 85% already tried conventional meds**

Educational Program offering Seminars/Webinars for:

- **Healthcare professionals/**
- **Patients**
- **Cannabis Industry**
- **Law enforcement**
- **Social Workers**

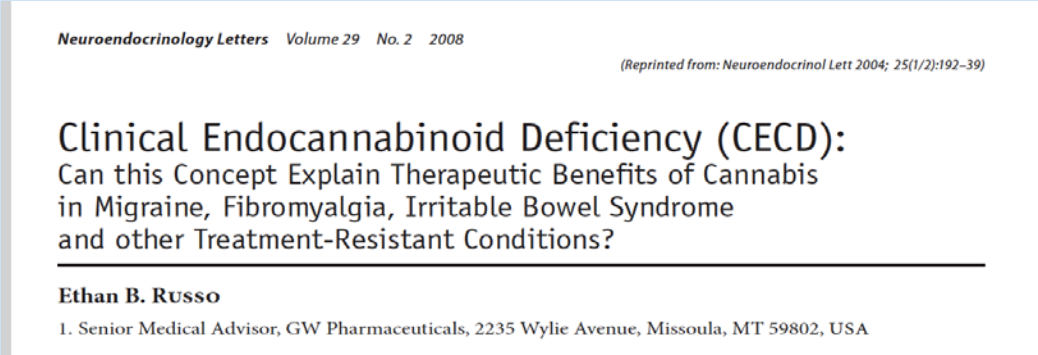
Cannabis Research



Number of publications in PubMed between 1960-2014 related to cannabis research

Hurd, et al, 2015

Endocannabinoid Deficiency



Neuroendocrinology Letters Volume 29 No. 2 2008

(Reprinted from: Neuroendocrinol Lett 2004; 25(1/2):192–39)

Clinical Endocannabinoid Deficiency (CECD): Can this Concept Explain Therapeutic Benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome and other Treatment-Resistant Conditions?

Ethan B. Russo

1. Senior Medical Advisor, GW Pharmaceuticals, 2235 Wylie Avenue, Missoula, MT 59802, USA

Endocannabinoid deficiency/dysfunction has since been implicated in the following medical conditions:

- Migraine headaches
- Fibromyalgia
- Multiple Sclerosis
- Irritable Bowel Syndrome
- Schizophrenia
- Huntington’s disease
- Autism Spectrum Disorder
- Anorexia
- Chronic motion sickness
- Seizure Disorders
- Anxiety
- Depression
- Parkinson’s disease
- ADD/ADHD
- Failure to Thrive/obesity

Plasma anandamide concentrations are lower in children with autism spectrum disorder

Debra S. Karhson, Karolina M. Krasinska, Jamie Ahloy Dallaire, Robin A. Libove, Jennifer M. Phillips, Allis S. Chien, Joseph P. Garner, Antonio Y. Hardan and Karen J. Parker

Molecular Autism Brain, Cognition and Behavior 2018 9:18
https://doi.org/10.1186/s13229-018-0203-y

Front. Pharmacol., 24 April 2018 | https://doi.org/10.3389/fphar.2018.00420

Emerging Role of (Endo)Cannabinoids in Migraine

Pinja Leimuranta[1], Leonard Khiroug[2,3]* and Rashid Giniatullin[1,4]*

[1]A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland
[2]Neurotar Ltd., Helsinki, Finland
[3]Neuroscience Center, University of Helsinki, Helsinki, Finland
[4]Laboratory of Neurobiology, Kazan Federal University, Kazan, Russia

Cellular and Molecular Life Sciences
August 2018, Volume 75, Issue 15, pp 2793–2811 | Cite as

Control of excessive neural circuit excitability and prevention of epileptic seizures by endocannabinoid signaling

Authors Authors and affiliations

Yuki Sugaya, Masanobu Kano

REVIEW

The endocannabinoid system as a target for the treatment of motor dysfunction

Javier Fernández-Ruiz

PERSPECTIVE ARTICLE

Front. Behav. Neurosci., 09 August 2013 | https://doi.org/10.3389/fnbeh.2013.00100

The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder (PTSD)

Viviana Trezza[1]* and Patrizia Campolongo[2]*

Translational Psychiatry

Original Article | OPEN | Published: 08 July 2014

Central anandamide deficiency predicts stress-induced anxiety: behavioral reversal through endocannabinoid augmentation

R J Bluett, J C Gamble-George, D J Hermanson, N D Hartley, L J Marnett & S Patel

Translational Psychiatry 4, e408 (2014) | Download Citation

Review articles from the 5th International Meeting of the IASP Special Interest Group on Neuropathic Pain (NeuPSIG)

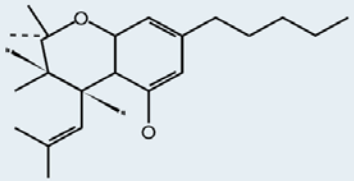
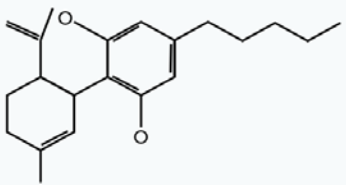
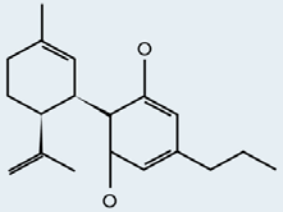
PAIN

The endocannabinoid system and neuropathic pain

Rafael Maldonado*, Josep Eladi Baños, David Cabañero

Phytocannabinoid Targets

Friedman, Daniel, and Orrin Devinsky. “Cannabinoids in the treatment of epilepsy.” New England Journal of Medicine 373.11 (2015) 1048-1058.

Cannabinoid	Structure	Central Nervous System Targets	Actions
Δ^9-Tetrahydrocannabinol		CB_1R CB_2R (microglia) TRPA1 TRPV2 TRPM8 $\alpha_1\beta$ GlyR 5-$HT_{3A}R$ PPAR-γ GPR18 GPR55	Partial agonist Partial agonist Agonist Agonist Antagonist Enhancer Antagonist Activator Agonist Agonist
Cannabidiol		CB_1R CB_2R (microglia) GPR55 TPRA1 TRPV1–3 TRPV4 TRPM8 5-$HT_{1A}R$ 5-$HT_{3A}R$ α_3GlyR PPAR-γ Ca_v3 ion channel Adenosine reuptake	Antagonist Antagonist Antagonist Agonist Agonist Agonist Antagonist Enhancer Antagonist Enhancer Activator Inhibitor Inhibitor
Cannabidivarin		TRPA1 TRPM8 TRPV4 TRPV1–3 DAGL-α	Agonist Antagonist Agonist Agonist Inhibitor

Epilepsy and ECS dysfunction

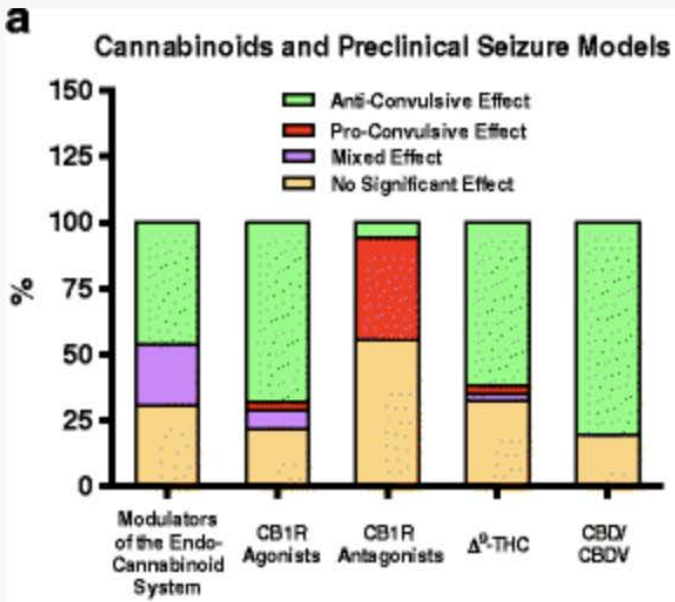
Compelling scientific evidence of ECS dysfunction leads to seizures

- Epileptic human brain tissue shows 60% reduction of endocannabinoids (Ludanyi, et al. 2008)
- Blockage of the CB1 receptor produced status epilepticus (Wallace, et al. 2003, Deshpande, et al. 2007)
- CSF endocannabinoids reduced in patients with untreated newly diagnosed temporal lobe epilepsy (Romigi, et. al. 2010)

- **Endocannabinoids play an intrinsic protective role in calming neuroexcitation**

Devinsky et al. “Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders.” *Epilepsia* 55.6 (2014): 791-802

Epilepsy and Cannabinoids: Preclinical Evidence



	Modulators of the Endo-cannabinoid System	CB1R Agonists	CB1R Antagonists	Δ^9-THC	CBD/ CBDV
# of Species	3	2	3	6	2
# of Discrete Conditions/ Models	13	69	18	34	41
Anti-convulsant	6 (46.2%)	47 (68.1%)	1 (5.6%)	21 (61.8%)	33 (80.5%)
Pro-convulsant	0 (0%)	2 (2.9%)	7 (38.9%)	1 (2.9%)	0 (0%)
Mixed Effect	3 (23.1%)	5 (7.2%)	0 (0%)	1 (2.9%)	0 (0%)
No Significant Effect	4 (30.8%)	15 (21.7%)	10 (55.6%)	11 (32.4%)	8 (19.5%)

Rosenberg, Evan C., et al. “Cannabinoids and epilepsy.” Neurotherapeutics 12.4 (2015): 747-768.

CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience

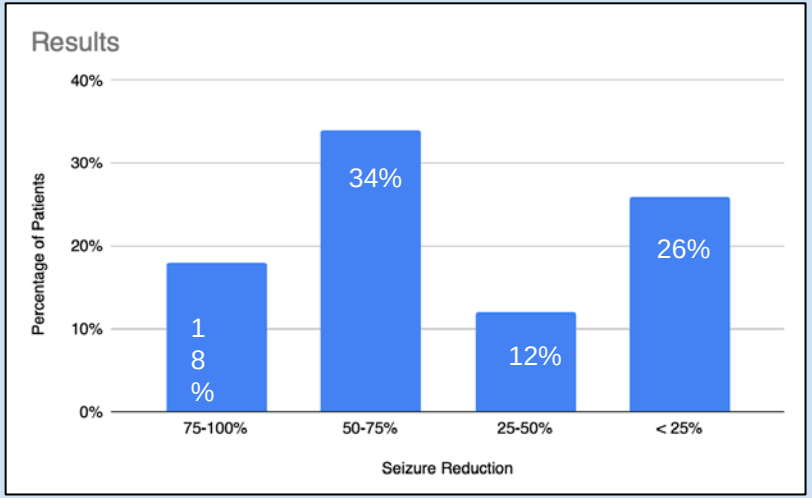
20:1 CBD:THC ratio whole plant

- 74 patients, all resistant to >7 AEDs, 66% failed Keto/VNS/both
- CBD Dose 1-20 mg/kg/day
- 3-12 months of treatment

Overall 89% reported seizure reduction

- 1 patient became seizure free
- 5 patients withdrew due to SE

- Improved behavior, alertness, language, communication, motor skills, sleep
- Adverse side effects: increased sz (7%), fatigue/sedation, GI irritation



Tzadok, et al. “CBD-enriched medical cannabis for intractable pediatric epilepsy: the current Israeli experience.” Seizure 35 (2016): 41-44.

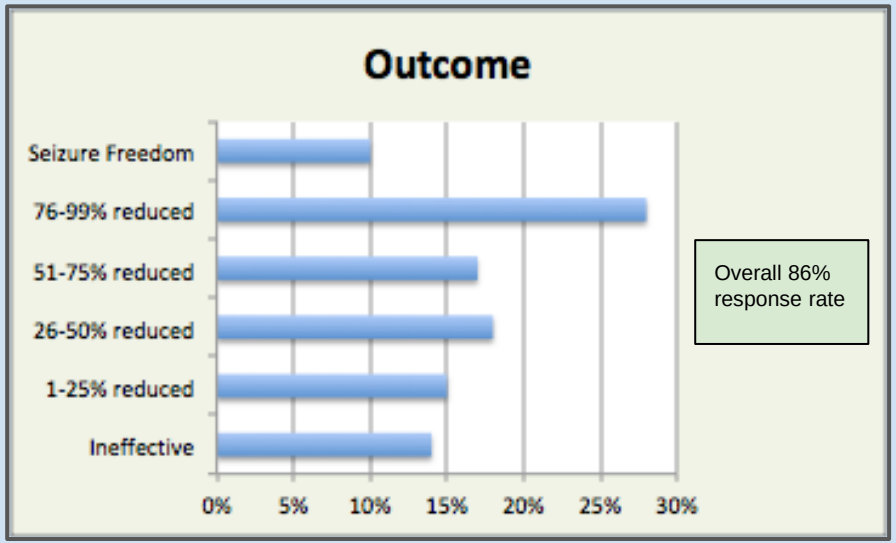
Contents lists available at ScienceDirect

Epilepsy & Behavior

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

The current status of artisanal cannabis for the treatment of epilepsy in the United States

Dustin Sulak [a,*], Russell Saneto [b], Bonni Goldstein [c]



- **272 combined patients from Washington and CA**
- **CBD +/- THC +/- THCA**
- **Beneficial SE:**
  - **Increased alertness**
  - **Better sleep**
  - **Improved mood**
  - **Less rescue medication used**
  - **Less ER/hospitalizations**
- **Adverse SE mild and infrequent - sedation**

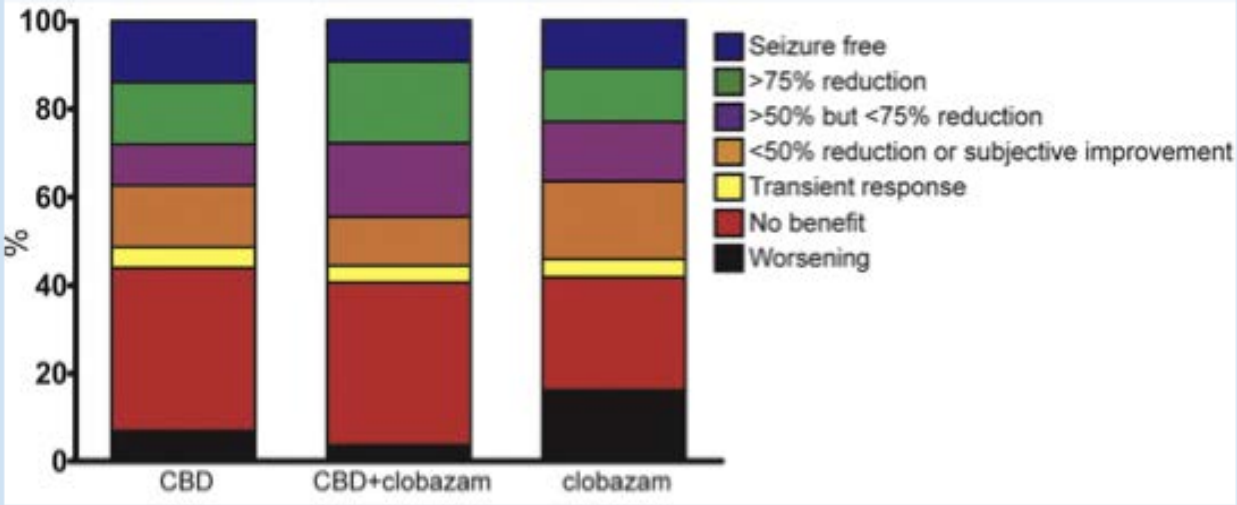
Epilepsy & Behavior

Volume 80, March 2018, Pages 240-246

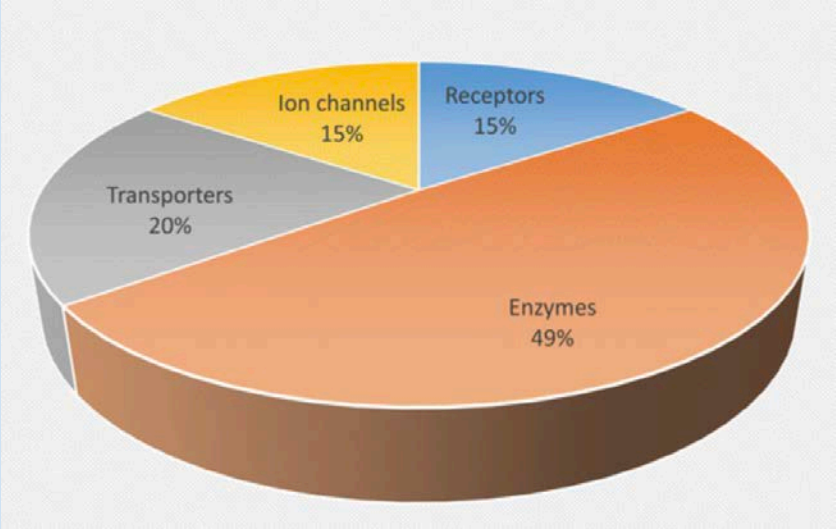
Efficacy of artisanal preparations of cannabidiol for the treatment of epilepsy: Practical experiences in a tertiary medical center

Giulia S. Porcari [a, 1], Cary Fu [b, 1], Emily D. Doll [b], Emma G. Carter [b], Robert P. Carson [b]

- Observational study of 108 pts
- **The addition of CBD resulted in 39% of patients having a > 50% reduction in seizures, with 10% becoming seizure-free.**
- CBD side effect: sedation (<4%)
- Benefits of increased alertness and verbal interactions more marked in CBD alone group



How does CBD work?



Bih, et al. "Molecular targets of cannabidiol in neurological disorders." *Neurotherapeutics* 12.4 (2015): 699-730.

65 known molecular targets

Receptors:
- Cannabinoid
- Glycine
- GPR18
- GPR55 **
- 5HT1A/2A
- PPAR
- GABA **
- Adenosine

Transporters:
- Anandamide uptake **
- Dopamine uptake
- Glutamate uptake
- Choline uptake

Enzymes:
- CYP450
- AANAT
- COX/LOX
- Mitochondrial Electron Transport Chain

Ion Channels
- TRP Channels (TRPV1-4, TRPM8)**
- VDAC, VGCC, VGSC **

AED - CBD Drug Interactions (Epidiolex studies)

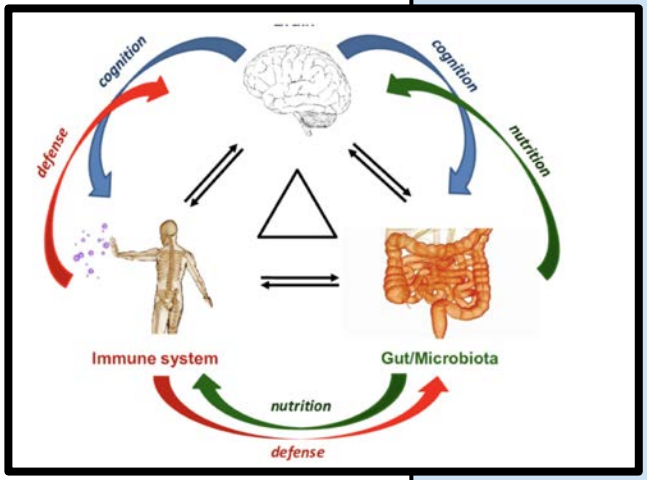
- **39 adults + 42 children treated with CBD (5 → 50 mg/kg/day) with baseline AED levels, repeated at follow-up visits (Gaston, et al. 2018)**
  - Increases in topiramate, rufinamide, N-CLB
  - Decrease in clobazam as CBD dose increased
  - In adults, zonisamide and eslicarbazepine increased
  - All increases were **within accepted therapeutic range except clobazam and N-CLB**
  - Increased liver function tests in patients on valproate

- **34 children with Dravet syndrome on pharmaceutical CBD tested before CBD and at 4 weeks (Devinsky, et al. 2018)**
  - Increase clobazam metabolite (N-CLB)
  - No change in levels of valproate, levetiracetam, topiramate
  - 6 patients on both CBD and valproate had elevated liver function tests (recovered)

Current dosing: 550 mg CBD /day (9.8 mg/kg/day)
plus 90 mg THC/day

Autism Spectrum Disorder

- **Prevalence 1 in 59 (CDC)**
- **Often comorbid with epilepsy, anxiety, ADHD, depression**



- **Main features include:**
  - **Communication difficulties**
  - **Repetitive behaviors**
  - **Social challenges (anxiety, tantrums, SIB)**

- **Neuro-inflammation & Neuro-immune abnormalities (Siniscalco, 2018)**
- **Gut issues 4 times more prevalent (McElhanon et al, 2014)**

Autism Spectrum Disorder

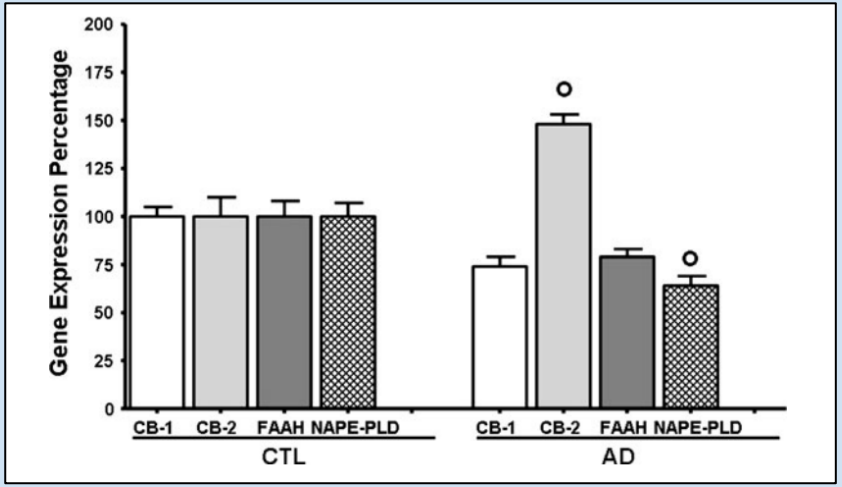
Literature review:

- **Case report of dronabinol in 6 year old boy: significantly decrease hyperactivity, irritability, lethargy, stereotypic movements and inappropriate speech on total daily dose of 3.6 mg (Kurz, et al, 2010)**
- **Link between two genetic mutations associated with autism and ECS deficit (Foldy, et al, 2013)**
- **Alterations of ECS in mice resulted in autistic-type behavioral abnormalities (Kerr, et al, 2013)**
- **Increased anandamide activity at CB1 receptors improves ASD-related social impairment (Wei, et al, 2016)**

Autism Spectrum Disorder

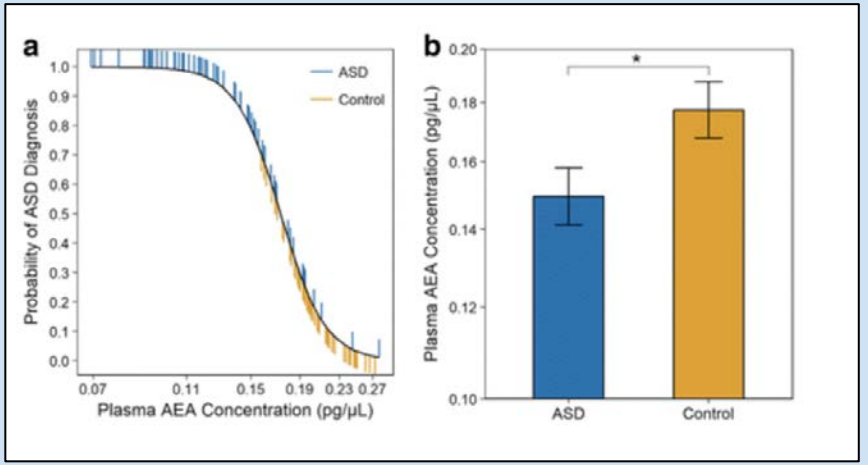
CB2 receptors up-regulated in white blood cells of children with autism

(Siniscalco, et al, 2013)



Plasma anandamide levels decreased in ASD such that anandamide concentrations significantly differentiated ASD cases

(Karhson, et al, 2018)



Cannabidiol Based Medical Cannabis in Children with Autism
(Aran, et al. *Neurology* 2018)

60 children with ASD -- ages 5-18 -- low functioning -- 83% boys -- severe behaviors

20:1 CBD:THC oil - starting dose CBD 1 mg/kg/day titrated up to max 10 mg/kg/day

- 52% responded
- 48% were given lower CBD:THC ratios (up to 6:1 with max dose of 5 mg/kg/day)
- 22% lower ratio much better, 12% slightly better, 10% no change, 5% worse

- **End of study: 73% still on treatment** (mean duration ~11 months)
- 27% stopped treatment: irritability, difficulty giving the oil, low efficacy +/- side effects

Range of dosing: CBD 0.1 - 6.4 mg/kg/day and THC 0.2 – 0.5 mg/kg/day

Cannabidiol Based Medical Cannabis in Children with Autism
(Aran, et al *Neurology* 2018)

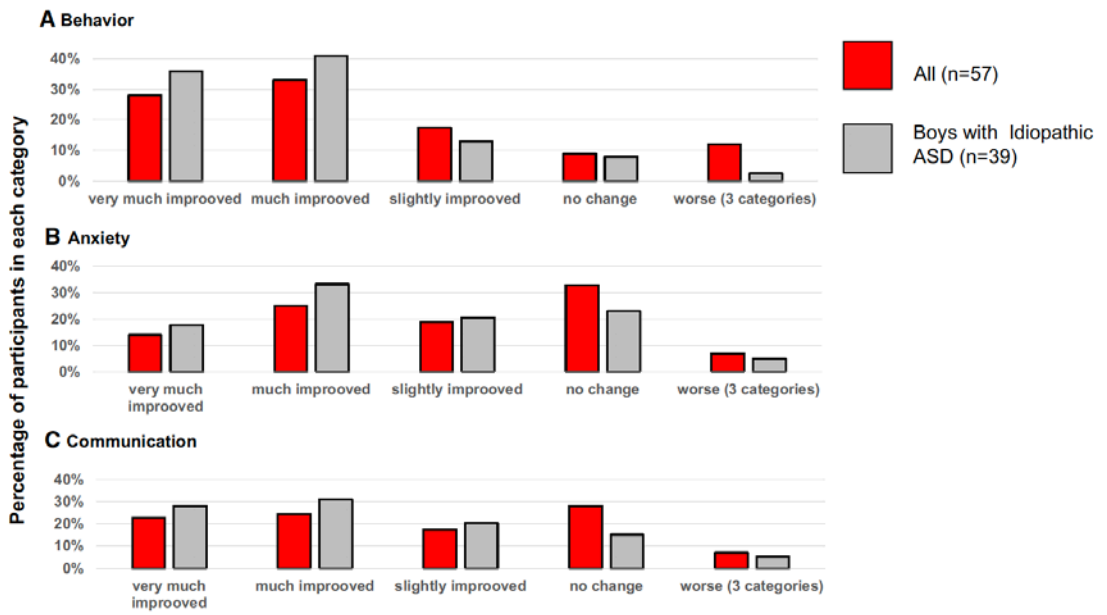


Fig. 1 Caregivers global impression of change in behavior anxiety and communication following cannabis treatment

Behavioral outbreaks: 61% much or very much improved

Improved anxiety: 39%

Improved communication: 47%

Less medication or lower doses: 33%

Stopped other medication: 24%

Added or increased meds: 8%

Lower circulating endocannabinoid levels in children with autism spectrum disorder

(Aran et al. *Molecular Autism* 2019)

EC LEVELS SUBSTANCIALLY LOWER IN CHILDREN WITH ASD

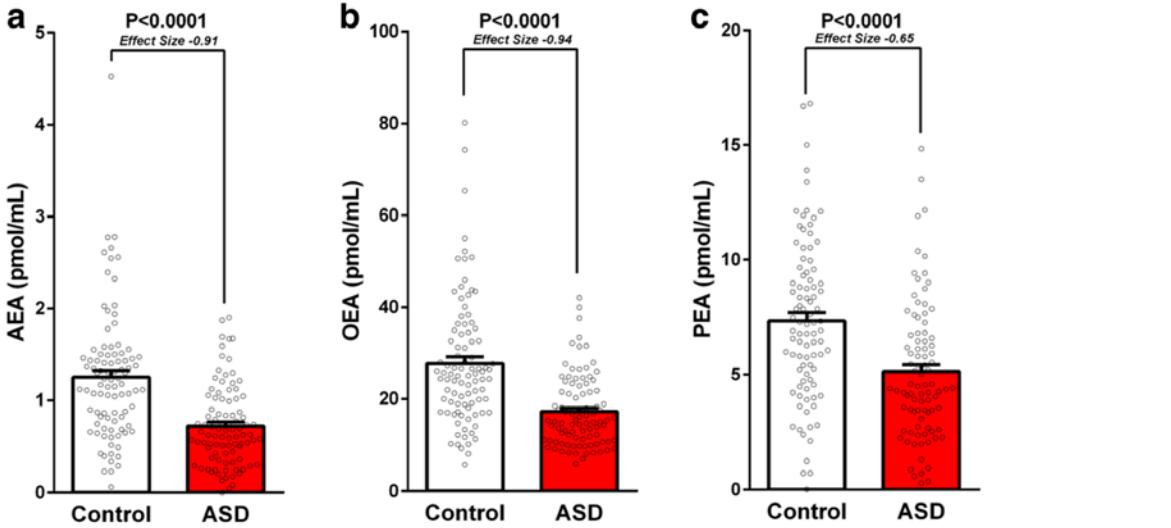


Fig. 1 Lower serum endocannabinoid levels in children with ASD. Legend: low endocannabinoid "tone" in serum samples of 93 children with ASD compared with 93 age- and gender-matched controls. Results of anandamide (AEA; panel **a**), oleoylethanolamine (OEA; panel **b**), and palmitoylethanolamide (PEA; panel **c**) are presented as mean, standard error, and distribution respectively

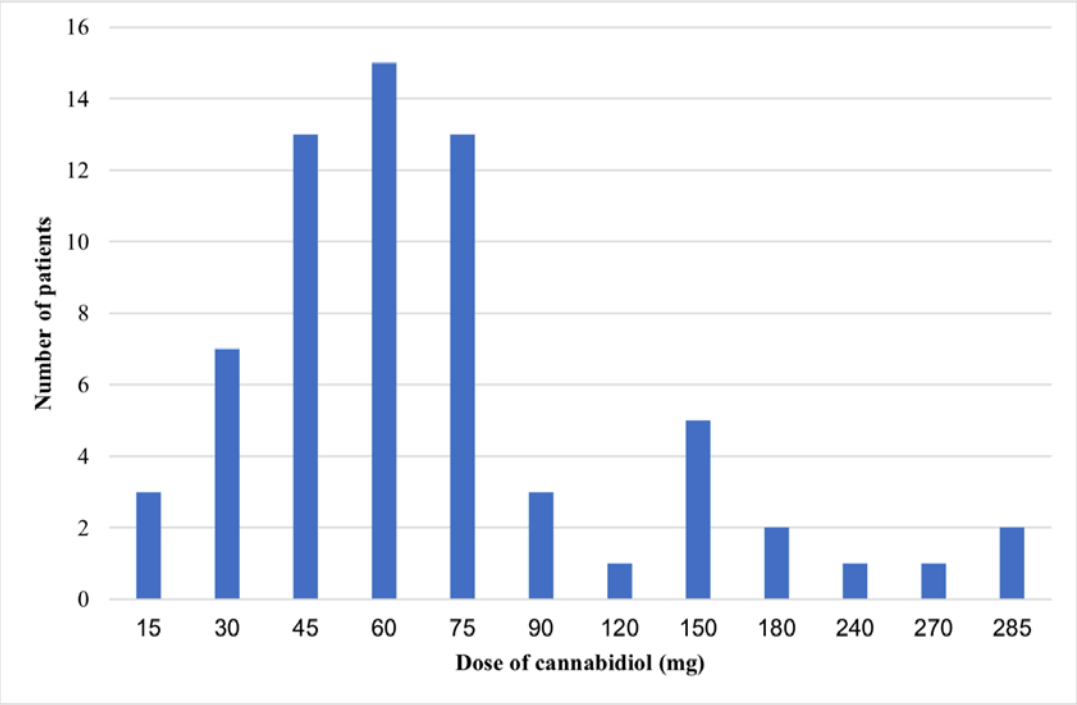
Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy
Schleider, et al. *Scientific Repo*rts (2019)

188 patients between 2015 -2017

- **Treatment for most was 20:1 ratio CBD:THC oil (whole plant)**
- **At 6 months: 82.4% (155) still in active treatment**

- 30.1% "significant improvement"
- 53.7% "moderate improvement"
- 6.4% "slight improvement"
- 8.6% "no change"
- 23 patients reported side effects – restlessness 6%, sleepiness 3%, intoxication 3%, increased appetite 3%, digestion issues 3%, dry mouth 2%, lack of appetite 2%
- Less than 5% discontinued due to SE
- **"Cannabis is safe, effective and well-tolerated for treatment of ASD"**

Supplementary figure S1: Distribution of cannabinoids consumptions. Total CBD (in mg) consumed at every intake by 66 patients receiving oil with 30% CBD and 1.5% THC. THC is 1/20 of the amount of CBD.



Most dosed three times a day

Schleider, et al 2019

	Intake prevalence Total (188)	Change at six months		
		Symptom disappeared	Improvement	No change or deterioration
Restlessness, No. (%)	170 (90.4)	1 (1.2)	71 (89.8)	7 (8.8)
Rage attacks, No. (%)	150 (79.8)	1 (1.3)	65 (89.0)	7 (9.5)
Agitation, No. (%)	148 (78.7)	1 (1.4)	57 (83.8)	10 (14.7)
Sleep problems, No. (%)	113 (60.1)	9 (19.5)	27 (58.6)	10 (21.7)
Speech Impairment, No. (%)	113 (60.1)	—	15 (30)	35 (70)
Cognitive impairment, No. (%)	91 (48.4)	—	15 (27.2)	40 (72.7)
Anxiety, No. (%)	69 (36.7)	—	24 (88.8)	3 (11.1)
Incontinence, No. (%)	51 (27.1)	2 (9.0)	7 (31.8)	13 (59.0)
Seizures, No. (%)	23 (12.2)	2 (15.3)	11 (84.6)	—
Limited Mobility, No. (%)	17 (9.0)	2 (18.1)	—	9 (81.8)
Constipation, No. (%)	15 (8.0)	1 (12.5)	6 (62.5)	2 (25)
Tics, No. (%)	15 (8.0)	1 (20.0)	4 (80.0)	—
Digestion Problems, No. (%)	14 (7.4)	1 (12.5)	5 (62.5)	2 (25.0)
Increased Appetite, No. (%)	14 (7.4)	1 (33.3)	1 (33.3)	1 (33.3)
Lack of Appetite, No. (%)	14 (7.4)	2 (40.0)	1 (20.0)	2 (40.0)
Depression, No. (%)	10 (5.3)	—	5 (100.0)	—

Table 2. Symptom prevalence and change. Symptom prevalence at intake in 188 patients assessed at intake and change at six months in patients responding to the six-month questionnaire.

Schleider, et al 2019

Phytocannabinoid Synthesis and Effects

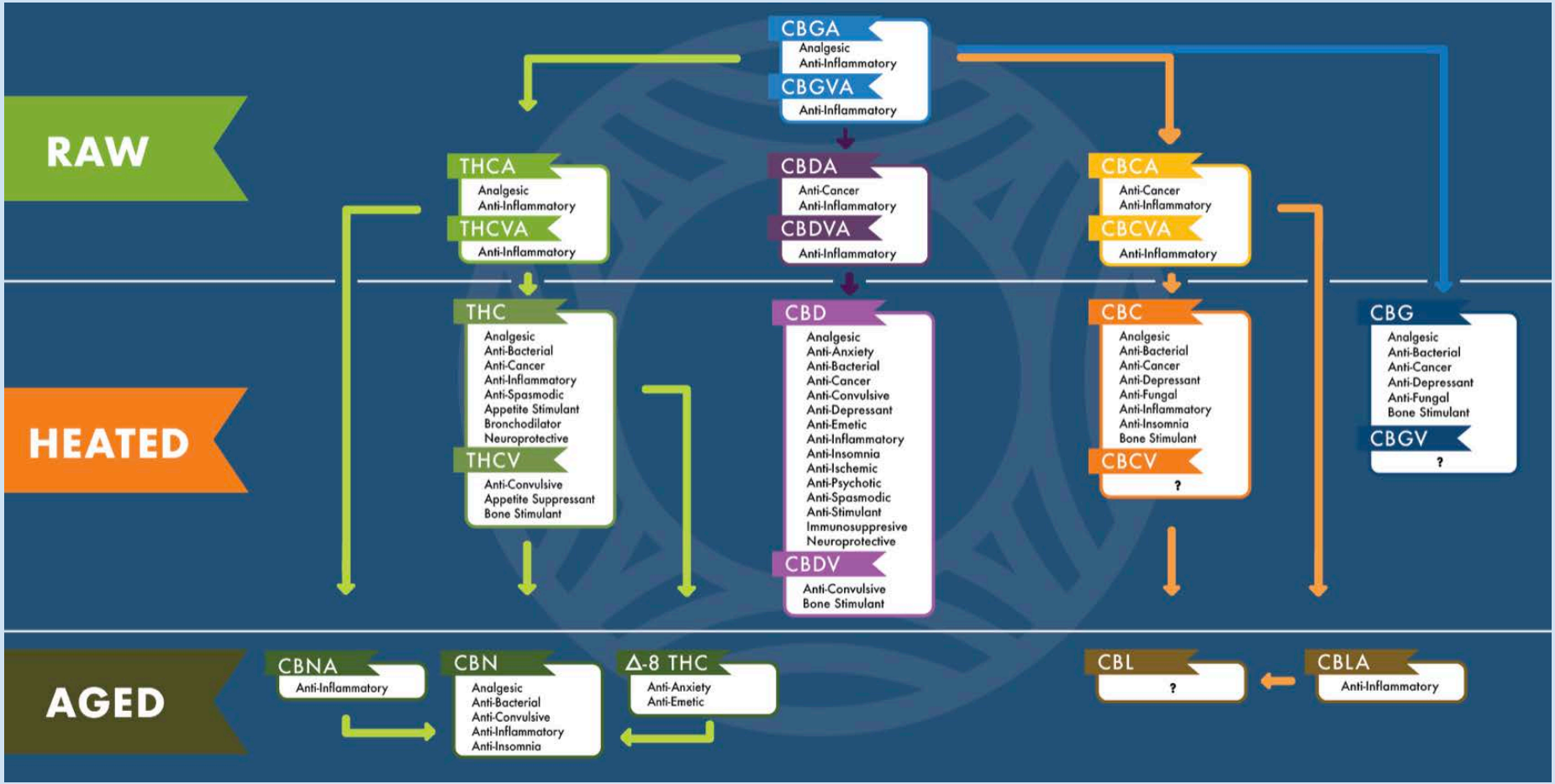


Image credit: echoconnection.org

Cannabinoid Medicines

- THC
- CBD
  - high ratio (27:1, 18:1, 10:1)
  - low ratio (4:1, 2:1, 1:1)
- THCA (THC acid)
- CBDA (CBD acid)
- CBG (cannabigerol)

Tested - Consistent batch to batch - Affordable – Accessible – Concentrated

Autism Case Report

17 year old girl with autism, anxiety, aggression, non-verbal, severe OCD, possible PCOS, no response to multiple medications

Started with **high-ratio CBD** at low doses and high doses (tried 3 products)

→ best dose response at 15 mg of 23:1 ratio once daily

Tried **THC** → best dose response at 2 mg THC once daily (tried 3 products)

Tried THCA → aggravated symptoms, discontinued use (tried 2 products)

Tried **CBG**→ best dose response at 6 mg once daily (tried 2 products)

Parents report ~ 60% less anxiety, quicker and easier transitions, happier, >90% reduction of aggression towards others, weaning Prozac

Thank you!