When Parents Ask About Cannabidiol in Autism Spectrum Disorders: Evidence or Anecdotal?

Gregory N. Barnes, MD, PhD
Department of Neurology
Executive Director
University of Louisville Autism Center
Louisville, KY

Faculty Name
Disclosures

- ***Research/Grants:*** GW Pharmaceutical/Greenwich Biosciences, Inc. (Clinical trial grant entitled: The Role of Cannabinoid Signaling in Autism and Epilepsy)

Learning Objective 1

Describe the function and components of the endogenous endocannabinoid system.

Learning Objective 2

Identify disease states using phytocannabinoid medications.

Learning Objective 3

Provide an overview of the current phytocannanbinoid data in autism spectrum disorders.

Cannabis Species

- Cannabis sativa – oldest known species used by humans (China)
  - >500 compounds: e.g. Eugenol: acts at GABAA receptors
  - 104 terpeno-phenol compounds, “cannabinoids”
- Cannabis indica – reference in Ancient Vedas text in India, ~ 1700 BCE
- Sativa usually ↑THC:CBD ratio (phytocannabinoids) v. indica
- Sativa more psychic and stimulatory
- Indica strains have more sedative properties

CBD = cannabidiol; GABBA = gamma (gamma)-aminobutyric acid; THC = tetrahydrocannabinol.

Endogenous Cannabinoids (Endocannabinoids (eCBs))

- Neuromodulatory lipids released by the postsynaptic membranes in response to neuronal activity
- Arachidonic acid derivatives produced by neurons and glia
- Principal eCBs (low in ASD: Aran et al, 2018; Karhson et al, 2018)
- 2-Arachidonoylglycerol (2-AG)
- Anandamide
- Hydrolyzed by fatty acid amide hydrolase (FAAH)
- CB Receptors – G-protein-coupled
- CB1 receptors (mainly CNS)
- CB2 receptors (mainly immune cells)

CNS = central nervous system.

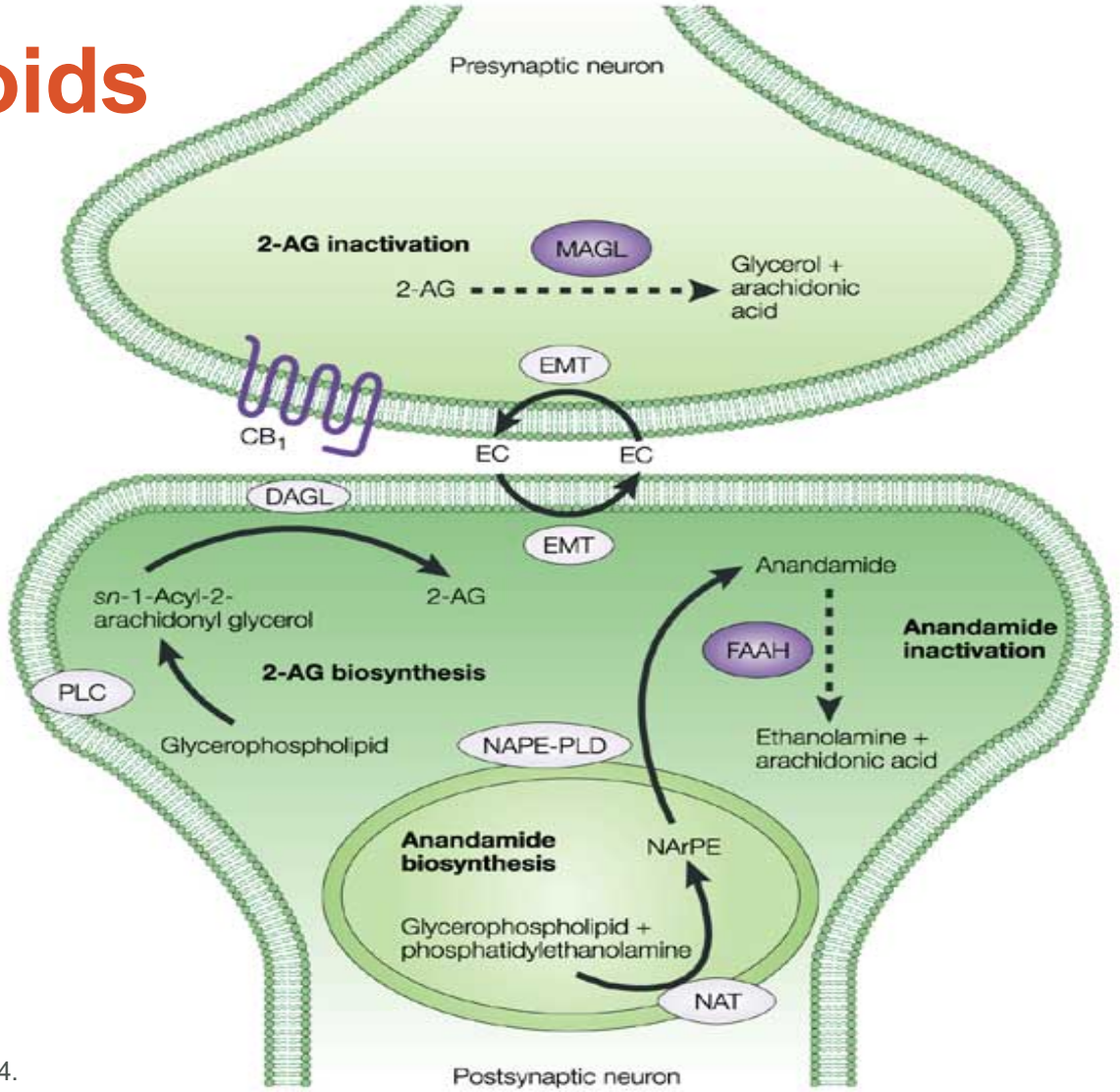
Aran A, et al. *Neurology.* 2018;90(15Suppl).; Karhson DS, et al. *Mol Autism*. 2018;9(18).; Wilson RI, Nicoll RA. *Science* 2002;296(5568):678-682.

Endocannabinoids (eCBs)

- -eCB production stimulated by:
  - Ca++ influx 2o to strong neuronal depolarization or burst firing
  - Activation of some Gq-coupled neurotransmitter receptors and glucocorticoid receptors
- eCBs modulate retrograde synaptic signaling
- Activation of CB1-R ↓'s neurotransmitter release
- CB1-R on GABAergic and glutamatergic axon terminals synapsing onto neurons whose axons project distally
- CB1 synaptic suppression is transient or longer lasting depending on pre/postsynaptic activity levels

GABA = gamma-aminobutyric acid.
Wilson RI, Nicoll RA. *Science* 2002;296(5568):678-682.

Endocannabinoids



AG = arachidonoylglycerol; EC = entorhinal cortex;
EMT = epithelial-to-mesenchymal transition;
FAAH = fatty acid amide hydrolase;
MAGL = monoacylglycerol lipase; NAPE-PLD = N-acyl phosphatidylethanolamine-specific phospholipase D;
NArPE = N-arachidonoylphosphatidylethanolamine;
PLC = phospholipase C.
Di Marzo V, et al. *Nat Rev Drug Discov* 2004;3(9):771-784.

Functions of ECS (AEA)

- Early in development AEA is tonically active, operating more as a promoter and regulator of neuronal development (i.e., axon pathfinding and synapse formation) rather than a retrograde messenger
- AEA has a pivotal role in the stress response postnatally
- Uptake of AEA is modulated by the concentration gradient created by AEA transport and subsequent intracellular degradation by the enzyme, fatty acid amide hydrolase (FAAH), localized at the endoplasmic reticulum

AEA = anandamide; ECS = electrocerebral silence.

Functions of ECS (2-Acylglycerol: 2-AG)

- 2-AG has a primary role as a retrograde messenger and is more abundant in the CNS (~200 times AEA)
- Mobilization of 2-AG is driven by levels of postsynaptic calcium and enzymatically synthesized by phospholipase C and diacylglycerol lipase-α
- Signaling of 2-AG is stable across development, but levels are strongly related to circadian rhythmicity and affected by sleep restriction
- Abundance, activity, and inactivation of 2-AG emphasize its role as a key modulator of neuronal excitability, synaptic transmission and plasticity

CB1R Localization

- CB1Rs are the most abundant GPCR in the brain and can be found at the highest expression levels in the olfactory bulb, hippocampus, basal ganglia, and cerebellum; areas implicated in ASD neuroanatomy
- CB1Rs are localized to the presynaptic terminal of gamma-aminobutyric acid (GABA) and glutamate neurons to act as feedback mechanisms controlling neurotransmitter release
- The role of CB1Rs in modulation of synaptic plasticity and neuronal excitability also mediates the euphorigenic effects of cannabis

ASD = autism spectrum disorder; GPCR = G protein-coupled receptors.

CB2R Localization

- CB2R was initially considered a ‘peripheral’ receptor as it was only observed in immune cells and peripheral tissues (i.e., heart, liver, adipose, bone, and the reproductive system)
- Recent evidence has identified CB2Rs in the CNS (particularly in microglia)
- Cancer, ulcerative colitis, diabetes, cancer, hypoxic-ischemic encephalopathy

ECS in Autism Spectrum Disorder

- Smith et al, 2017: Rare Genetic Variants of ECS Genes: CNR1, CNR2, DAGLA, MGLL, FAAH
- 6032 cases, 5000 controls
- Rare variants CNR1: associated with migraines, sleep disorders, memory disorders, anxiety
- Rare variants of DAGLA: associated with autism, seizures, broad NDD

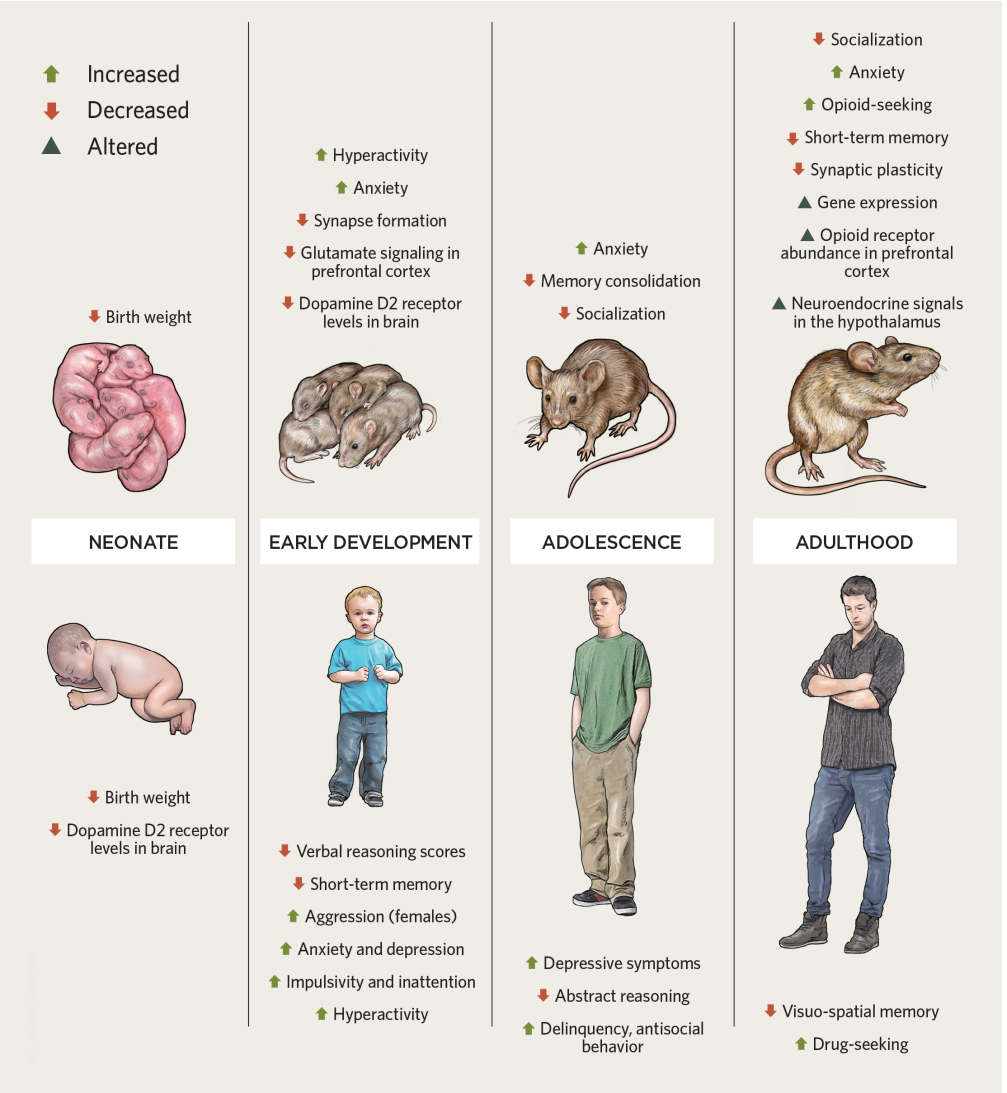
CNR = cannabinoid receptor; DAGLA = diacylglycerol lipase; FAAH = fatty acid amide hydrolase; NDD = neuro-developmental delay.
Smith DR, et al. *PLoS One*. 2017;12(11):e0187927.

ECS in Autism Spectrum Disorder

- Up-regulation of CB2R mRNA and protein levels, but not CB1R, in peripheral blood mononuclear cells was observed in a small (n = 17) paediatric (3-9 years old) autistic cohort in comparison to age-matched typically developing controls
- In peripheral blood mononuclear cells, the NAPE-PLD mRNA levels (AEA synthesis enzyme) in autistic participants were also significantly decreased
- Lower circulating anandamide (AEA) was observed in plasma from 59 autistic children (aged 3–12 years) in comparison to 53 age- and IQ-matched neurotypical controls (Karhson et al, 2018)
- This result was independently replicated and extended by Aran et al, 2018 in a larger, older (aged 6–21 years) cohort, where autistic children had lowered AEA

mRNA = messenger ribonucleic acid.
Karhson DS, et al. *Mol Autism* 2018;9:18.; Aran A, et al. *Neurology.* 2018;90(Suppl15).

- Exposure to synthetic cannabinoids and THC during pregnancy increases risk of ASD and schizophrenia in offspring

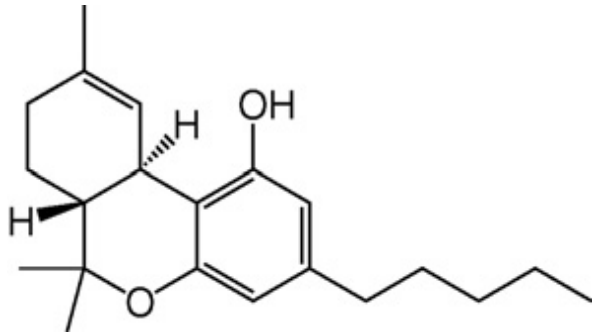


Scheyer A, O'Keefe L. The Scientist. 2018. https://www.the-scientist.com/infographics/infographic--how-exposure-to-cannabis-in-utero-affects-development-65266?_ga=2.255134721.848593769.1546875121-766682835.1527825500. Accessed February 25, 2020.

Exogenous Cannabinoids

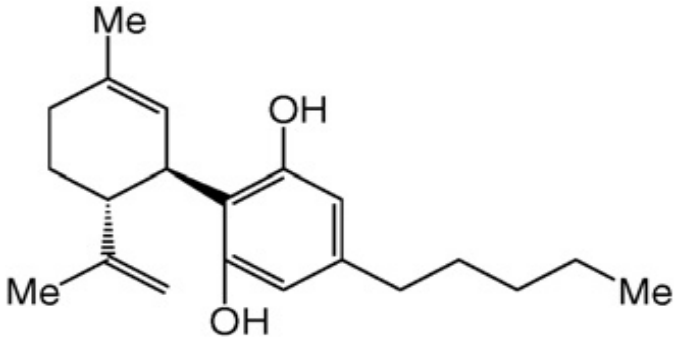
Δ^9 Tetrahydrocannabinol (THC)

- Psychoactive
- CB1 agonist



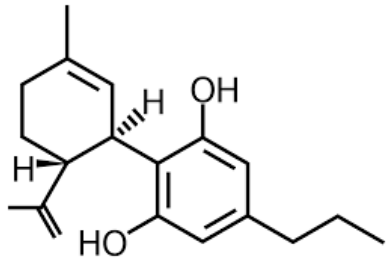
Cannabidiol (CBD)

- Non-psychoactive
- Very slight CB1/CB2 indirect antagonist; opposes some CNS effects of THC
- Antagonist at GPR55 receptor, ? CBD receptor



Cannabivarin (CBDV)

- CBD and CBDV are homologues, differing only in the length of the C3 alkyl side-chain (CBD:C5H11, CBDV:C3H7)



- The shorter side-chain of CBDV leads to decreased receptor binding affinity and lowered potency
- However, beyond its anti-convulsant effects, little is known about CBDV definitively
- Small clinical studies and animal models suggest impacts on social and language function

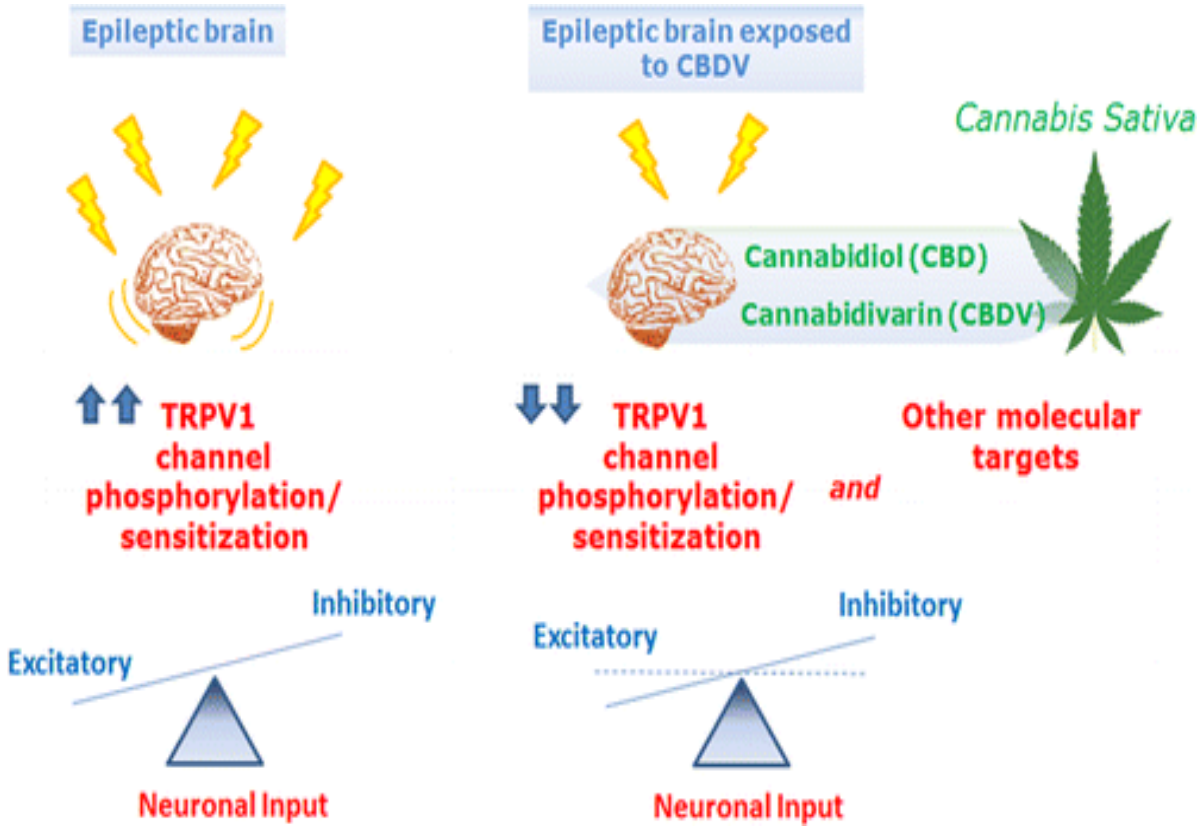
CBD: Mechanisms of Action

- G-protein-coupled receptor GPR55 antagonist: ↓presynaptic Ca++ release[1]
- Inhibit the degradation (FAAH) and reuptake of anandamide, ↑ECs[2]
- Equilibrative nucleoside transporter
- 5-HT1a receptor
- Neuroprotective and anti-inflammatory effects
- Alters Ca2+ flux[2-5]

Ca = calcium; Ca++ = myocyte calcium.

1. Sylantyev S, et al. *PNAS.* 2013;110(13):5193-5198.; 2.Bisogno T, et al. *Br J Pharmacol*. 2001;134(4):845-852.;
3. De Petrocellis L, et al. *Br J Pharmacol*. 2011;163(7):1479-1494.; 4. Qin N, et al. *J Neurosci.* 2008;28(24):6231-6238.; 5. Whalley with permission.

End Results of Phytocannabinoid Treatment



TRPV1 = transient receptor potential cation channel subfamily V member 1.

Real Life Experience with Medical Cannabis in Patients with ASD

- Bar-Lev Schneider, Mechoulaum, Saban, Meiri, and Novack published in *Scientific Reports* 2019
- Treated 188 pediatric patients (average age 12-years) with cannabis plant extract 2015-2017
- Dosing range wide (difficult from report)
- No standard questionnaires
  - Parent report: Improved Yes or No?
  - Quality of life assessed on a Likert scale
    - Very poor to poor, neither poor nor good, good to very good

Bar-Lev Schleider L, et al. *Sci Rep*. 2019;9(1):200.

Real-Life Experience with Medical Cannabis in Patients with ASD

- Response rate for aggression, sleep, seizures, anxiety, speech cognition, tics (30-50% improvement)
- Side effects– restlessness, sleepiness, psychoactive effects, digestion problems/lack of appetite

Bar-Lev Schleider L, et al. *Sci Rep*. 2019;9(1):200.

Oral Cannabidiol/THC Use in Children with ASD and Related Comorbidities

- Barchel, Stolar, De-Haan, Ziv-Baran, Saban, Fuchs, Koren, and Berkovitch, 2019
- Open label with 53 children (4-22 years)
- Treated with plant derived 30% CBD and 1.5% THC for median 66 days (30-588)
- Dose 16 mg/kg/d (max dose 600 mg/d) CBD and 0.8 mg/kg/d of THC (max dose 40 mg/d)

Barchel D, et al. *Front Pharmacol*. 20199:1521.

Oral Cannabidiol/THC Use in Children with ASD and Related Comorbidities

- No standard questionnaires (no change, improved, worsened)
- 30% improvement in self-injury and rage attacks, hyperactivity, and sleep problems
- Side effects did include somnolence and decrease appetite

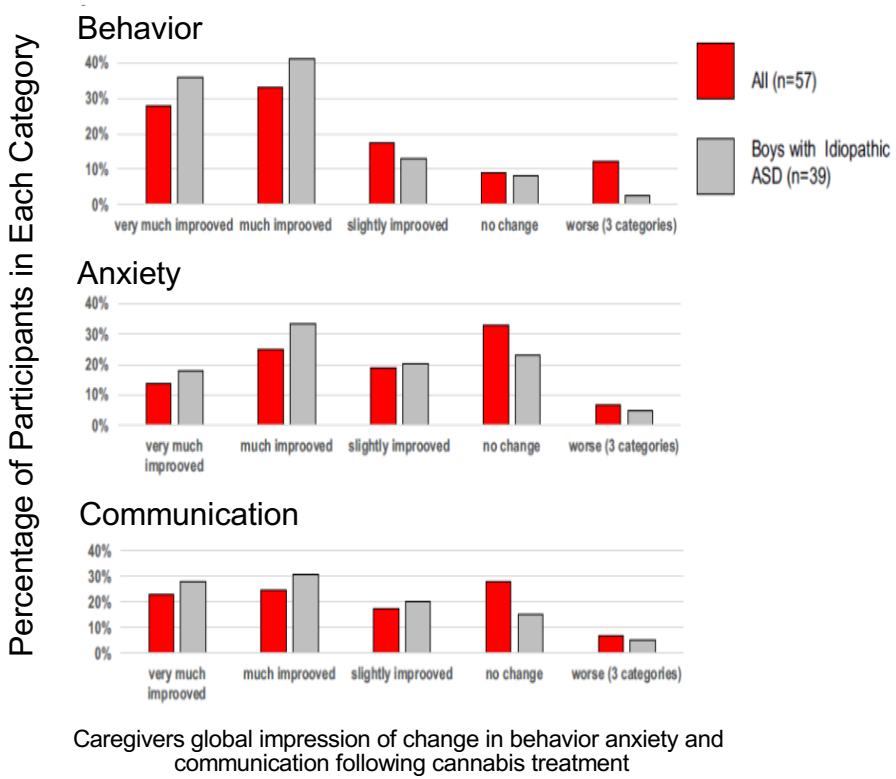
Barchel D, et al. *Front Pharmacol*. 20199:1521.

Open Label Studies of CBD in Patients with ASD: Dr Aran

- Aran, Cassuto, Lubotzky, Wattad, Hazan published in *JADD* 2019
- Open label 60 children (age 5-18 years, avg 12 years) for 7-13 months (73% retention rate
- 77% had lower cognitive function
- Treated with plan extract of CBD/THC 20:1.
- Titrated 2-3 weeks (from 1 to 10 mg/kg/d CBD)

Aran A, et al. *J Autism Deve Disorder* 2019;49(3):1284-1288.

Open Label Studies with CBD in Patients with ASD: Dr Aran



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

- 50% did not respond initially to higher ratio
- Those 29 subjects were offered lower ratio (6:1). Thirteen reported improvement on lower ratio CBD/THC
- Adverse events: sleep disturbances, loss of appetite, mood changes, somnolence, psychosis

Aran A, et al. *J Autism Deve Disorder* 2019;49(3):1284-1288.

Dr Aran: RCT with THC/CBD

- NCT02956226 was a phase 2, proof of concept trial, conducted in a single referral center - Shaare Zedek Medical Center, Jerusalem, Israel
- In this double-blind, placebo-controlled trial, 150 children (age 5-21 years) with ASD and behavioral problems (Clinical Global Impression of Severity ≥ 4), have been randomized (in a 1:1:1 ratio) to receive either placebo or one of two cannabinoid solutions for 12 weeks

Aran A, Cayam-Rand D. *Rambam Maimonides Med J*. 2020;11(1):e0003.

Dr Aran: RCT with THC/CBD

The cannabinoid solutions were:

- Whole plant cannabis extract containing cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) in a 20:1 ratio
- Purified CBD and THC in the same ratio and dose but without other components of the cannabis plant such as minor cannabinoids, terpenes, and flavonoids, that might also contribute to the therapeutic effect in an entourage effect

Aran A, Cayam-Rand D. *Rambam Maimonides Med J*. 2020;11(1):e0003.

Dr Aran: RCT with THC/CBD

- Two co-primary outcomes were designated to assess improvement in disruptive behaviors following cannabinoid treatment:
  - A patient and family-centered clinician assessment (Clinical Global Impression-Improvement scale (CGI-I))
  - A parent questionnaire (Home Situations Questionnaire–Autism Spectrum Disorder (HSQ-ASD))

Aran A, Cayam-Rand D. *Rambam Maimonides Med J*. 2020;11(1):e0003.

Dr Aran: RCT with THC/CBD

- In the CGI-I, 43% of the children were either much or very much improved following cannabinoid treatments compared to 21% on placebo (n = 137; *p* = .009)
- In the HSQ-ASD, a relatively high placebo effect was observed (46%), which did not differ significantly from the rate of clinically significant improvement after cannabinoids (53%; n = 121)

Aran A, Cayam-Rand D. *Rambam Maimonides Med J*. 2020;11(1):e0003.

Dr Aran: RCT with THC/CBD: Exploratory Outcomes

- Intriguingly, 44% of participants had a clinically significant improvement in the SRS-2 score after cannabinoids compared to 19% after placebo (n = 98; *p* = .013)
- In the APSI, 44% of participants had a clinically significant improvement in the score after cannabinoids compared to 26% after placebo (n = 122; *p* = .054)

APSI = Autism Parenting Stress Index; SRS-2 = Social Responsiveness Scale 2nd ed.
Aran A, Cayam-Rand D. *Rambam Maimonides Med J*. 2020;11(1):e0003.

Dr Aran: RCT with THC/CBD

Adverse events (AEs)

- AEs that were more common during cannabinoid treatment included:
  - Somnolence (19% mild and 6% moderate during the cannabinoid treatment compared to 8% mild during the placebo)
  - Decreased appetite (19% mild and 4% moderate during the cannabinoid treatment compared to 13% mild and 2% moderate during the placebo)

Aran A, Cayam-Rand D. *Rambam Maimonides Med J*. 2020;11(1):e0003.

Safety and Tolerability of GWP42006 (CBDV) in Subjects with Drug Resistant Epilepsy and Autism Spectrum Disorders

- Gregory Barnes, Janice Sullivan, and Lonnie Sears
  - University of Louisville Autism Center
- Kevan VanLandingham, Volker Knappertz, and Geoffrey Guy
  - GW Research LTD

Clinical Problems

- Autism spectrum disorder (ASD) is a complex condition that can be defined as a group of diverse neurodevelopmental disorders
- Epilepsy and autism have been estimated to coexist in 20-30% of patients with either disorder[1]
- Only 8-10% of autism and epilepsy subjects treated with anti-seizure drugs (AEDs) have sustained cognitive and behavioral improvements

1. Barnes G, et al. American Epilepsy Society 72nd Annual Meeting. 2018. New Orleans, LA. Abstract No. 3.288.

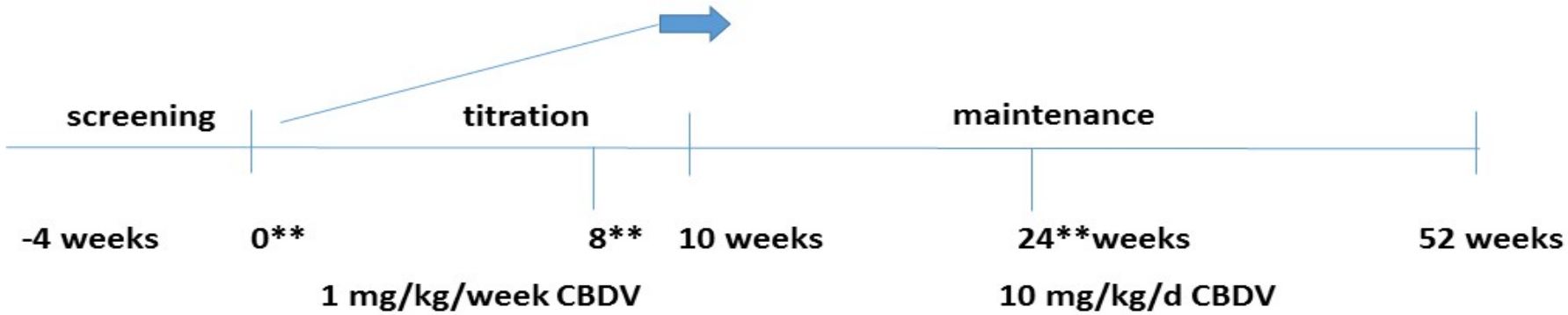
Clinical Characteristics of Autism and Epilepsy Subjects

- An expanded access protocol (IND: 128395) was developed and an initial pilot cohort of 6 subjects (ages 6-18 years, IQs 30-50) with documented autism and drug resistant epilepsy (no epileptic encephalopathy) were recruited to treat with CBDV
- ADOS severity score was an average of 7 (range 4-10) and the baseline 2-week seizure frequency was 15 (range 2-50)

ADOS = Autism Diagnostic Observation Schedule.

Barnes G, et al. American Epilepsy Society 72nd Annual Meeting. 2018. New Orleans, LA. Abstract No. 3.288.; GW Research Ltd. Safety and Tolerability of Cannabidivarin (CBDV) in Children and Young Adults With Autism Spectrum Disorder. ClinicalTrials.gov Identifier: NCT03849456. 2020.

Study Design



**At screening (week 0), week 8, and week 24, cognitive testing (DAS), language testing (MLU), autism testing (ADOS + PDD + BI +SCQ) sleep (actigraphy + CSHQ + PSG-EEG), motor (movement ABC), seizure diary, and adaptive/behavioral testing (Vineland, CBCL) were performed.

ABC = Assessment Battery for Children; BI = behavior inventory; CBCL = Child Behavior Checklist; EEG = Electroencephalography; MLU = mean length of utterance; PDD = pervasive developmental disorder; PSG = polysomnography; SCQ = Social Communication Questionnaire.

Barnes G, et al. American Epilepsy Society 72nd Annual Meeting. 2018. New Orleans, LA. Abstract No. 3.288.; GW Research Ltd. Safety and Tolerability of Cannabidivarin (CBDV) in Children and Young Adults With Autism Spectrum Disorder. ClinicalTrials.gov Identifier: NCT03849456. 2020.

Summary of CBDV Expanded-Access Protocol

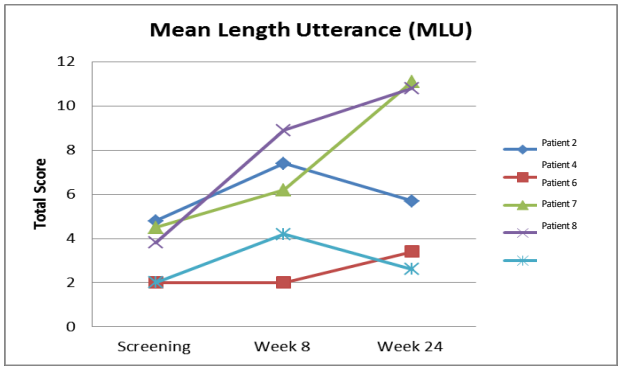
- 5 subjects (ages 6-18 years) with documented autism and epilepsy (≥ 2 countable seizures per month)
  - ADOS severity score was an average of 7 (range 4-10)
  - baseline 2-week seizure frequency was 15 (range 2-50)
- Titrated from 1 mg/kg/day to 10 mg/kg/day CBDV (GWP42006) in divided doses BID
- Assessments at weeks 8 and 24 include:
  - Children's Sleep Habit Questionnaire
  - Children Behavioral Checklist
  - VABS-II
  - Mean Length Utterance (MLU)
  - Differential Ability Scales
  - Social Communication Questionnaire
  - ADOS Calibrated Severity Score (ADOS-CSS)
  - Pervasive Developmental Disorder Behavioral Inventory
  - Motor battery

BID = twice a day.

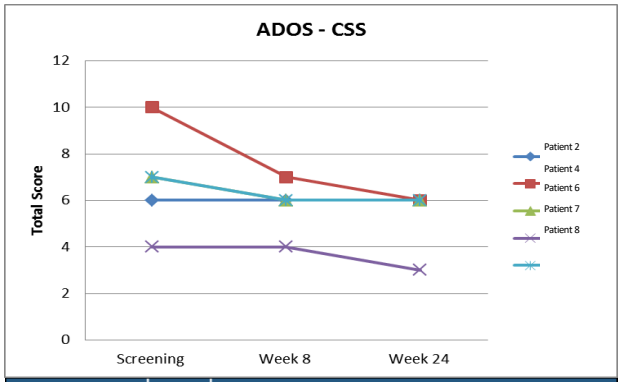
Barnes G, et al. American Epilepsy Society 72nd Annual Meeting. 2018. New Orleans, LA. Abstract No. 3.288.; GW Research Ltd. Safety and Tolerability of Cannabidivarin (CBDV) in Children and Young Adults With Autism Spectrum Disorder. ClinicalTrials.gov Identifier: NCT03849456. 2020.

Summary of CBDV Expanded-Access Protocol

- CBDV was well tolerated at 10 mg/kg/day dosing through 44 weeks; gastroesophageal reflux, aggression, and sedation were the most common adverse events
- At the 44-week time point 3 subjects with generalized epilepsy were seizure free
- Caretakers of all subjects report consistent gains in social engagement and communication regardless of seizure frequency
- Increased MLU score and a decreased ADOS-CSS at week 24:



Scale	N*	Baseline Mean (SD)	Change from baseline Wk 24 Mean (SD)	
MLU	5	3.9 (1.57)	3.3	(3.21)



Scale	N*	Baseline Mean (SD)	Change from baseline Wk 24 Mean (SD)	
ADOS-CSS	5	6.6 (2.15)	-1.4	(1.52)

Barnes G, et al. American Epilepsy Society 72nd Annual Meeting. 2018. New Orleans, LA. Abstract No. 3.288.; GW Research Ltd. Safety and Tolerability of Cannabidivarin (CBDV) in Children and Young Adults With Autism Spectrum Disorder. ClinicalTrials.gov Identifier: NCT03849456. 2020.

Conclusions of CBDV Autism-Epilepsy Study

- Initial data at 44-104 weeks post exposure suggest GWP42006/CBDV is well tolerated and has produced no major laboratory anomalies
- Seizure reductions were greatest and most well sustained in those with generalized seizure semiology
- At 10 mg/kg/d CBDV for 44-104 weeks, 6 subjects have made non-significant trending but sustained increases in social and communications skills and decreased core autism scores via direct measures

Barnes G, et al. American Epilepsy Society 72nd Annual Meeting. 2018. New Orleans, LA. Abstract No. 3.288.; GW Research Ltd. Safety and Tolerability of Cannabidivarin (CBDV) in Children and Young Adults With Autism Spectrum Disorder. ClinicalTrials.gov Identifier: NCT03849456. 2020.

Conclusions of CBDV Autism-Epilepsy Study

- Cognitive and behavioral changes are likely not sensitive to seizure frequency
- Seizure control is very sensitive to dose
- Of note, dosing is taken with foods and drug producing side effects abated when AEDs were weaned

Barnes G, et al. American Epilepsy Society 72nd Annual Meeting. 2018. New Orleans, LA. Abstract No. 3.288.

Conclusion

- Endocannabinoid system plays a major role in brain development and function of brain regions relevant to ASD.
- Harm can be done with in utero exposure to phytocannabinoids. Psychosis is the most common serious postnatal event after exposure.
- Unlike conventional wisdom, phytocannabinoids are medications which should be monitored (CBC, CMP minimum) by clinicians familiar with these medications.
- Phytocannabinoids are well tolerated and show promise in autism clinical trials.
- Greater knowledge on toxicity, dosing, sensitive populations, combinations of medications, etc is needed.

#CBD2020

CBD2020 CONFERENCE

CME Outfitters

Exploring the Evidence for Medical Cannabis in Clinical Practice

February 26-27, 2020 | The LINQ | Las Vegas, Nevada

Provided by

CME Outfitters