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ASA is the largest national nonprofit organization of patients, medical cannabis providers, medical professionals, scientists and concerned citizens promoting safe and legal access to cannabis for therapeutic use and research with over 100,000 advocates in all 50 states.

Medical Cannabis in Autism and Epilepsy: Preclinical and Clinical Evidence

Dustin Sulak, DO

September 26, 2020

Disclosure

- Integr8 Health, owner – medical practices in Maine
- Healer, equity – patient education, industry training, consulting, extraction/formulation, hemp and medical cannabis products
- Zelira Therapeutics, paid medical advisor – biotech and research
- COR Analytics, paid medical advisor
- Society of Cannabis Clinicians, unpaid board of directors member – professional society

Cannabis in Autism Spectrum Disorders

International Journal of
Molecular Sciences

MDPI

Review

The Endocannabinoid System and Autism Spectrum Disorders: Insights from Animal Models

Erica Zamberletti [1,2,*], Marina Gabaglio [1] and Daniela Parolaro [1,2]

[1] Department of Biotechnology and Life Sciences (DBSV), University of Insubria, 21052 Busto Arsizio (VA), Italy; marina.gabaglio@uninsubria.it (M.G.); daniela.parolaro@uninsubria.it (D.P.)
[2] Zardi Gori Foundation, 20122 Milan, Italy
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Received: 24 July 2017; Accepted: 4 September 2017; Published: 7 September 2017

- ECS regulates:
  - social and emotional reactivity
  - learning and memory
  - seizure threshold
  - circadian rhythm regulation

ECS Dysregulation in Autism

- Reduced CB1 expression in postmortem brains of individuals with ASD (Purcell et al., 2001)
- Reduced ECS activity demonstrated in relevant brain regions of several ASD models:
  - Fragile X
  - Mouse neuroligin 3
  - BTBR mice
  - Rat valproic acid

Aran *et al. Molecular Autism* (2019) 10:2
https://doi.org/10.1186/s13229-019-0256-6

Molecular Autism

RESEARCH Open Access

Lower circulating endocannabinoid levels in children with autism spectrum disorder

Adi Aran[1*], Maya Eylon[2], Moria Harel[1], Lola Polianski[1], Alina Nemirovski[2], Sigal Tepper[3], Aviad Schnapp[1], Hanoch Cassuto[1], Nadia Wattad[1] and Joseph Tam[2]

- 93 children with ASD (age = 13.1 ± 4.1, range 6–21; 79% boys)
- 93 age- and gender-matched neurotypical children (age = 11.8 ± 4.3, range 5.5–21; 79% boys)

- Serum levels of 2-AG were not significantly different.
- Anandamide (AEA) has function similar to THC
- OEA and PEA have low affinity to CB1 and CB2 but activate PPARs and TRPV1, similar to CBD.
- No significant association w/ ADHD symptoms, ASD severity, comorbidity, and use of medications

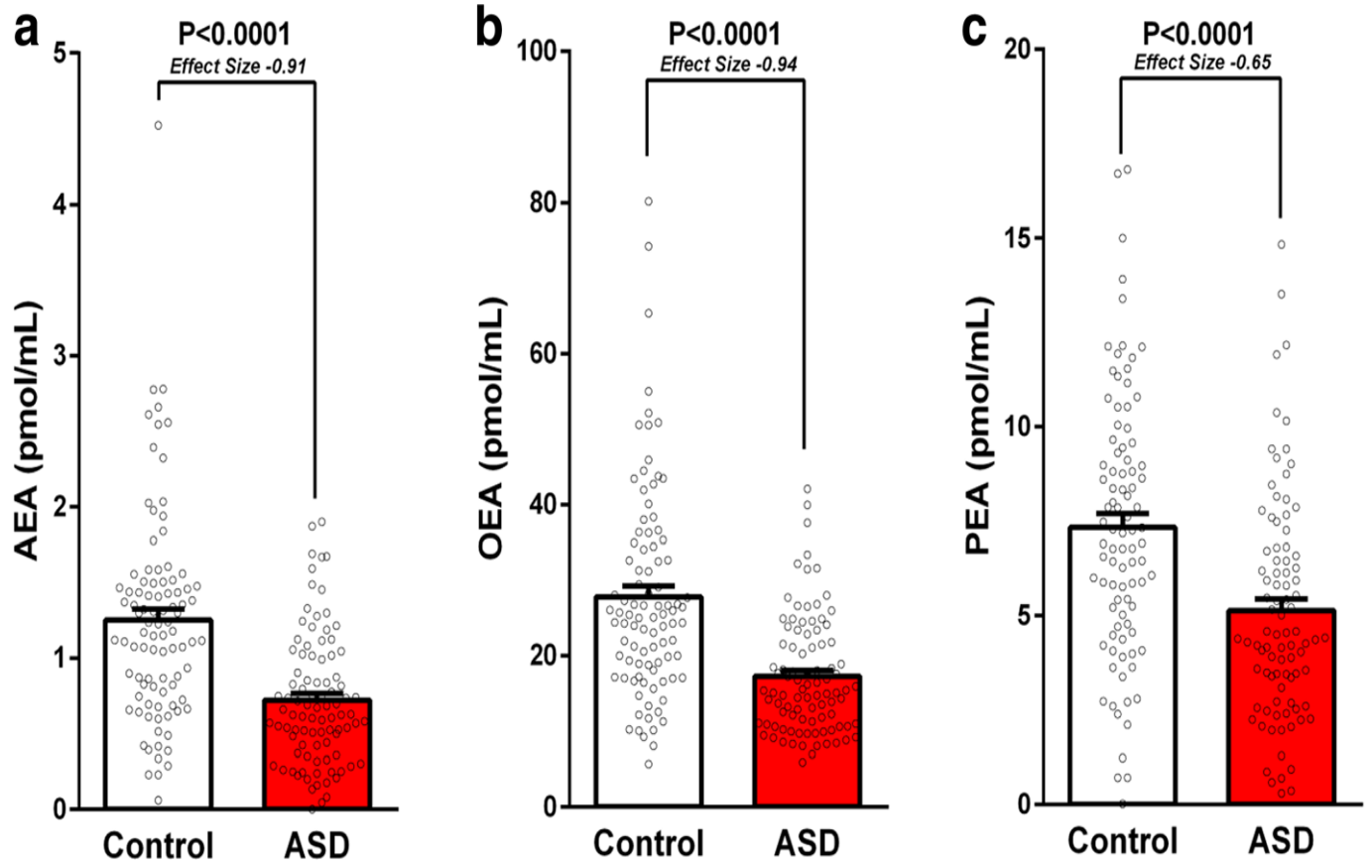


Fig. 1 Lower serum endocannabinoid levels in children with ASD. Legend: low endocannabinoid "tone" in serum samples of 93 children with ASD compared with 93 age- and gender-matched controls. Results of anandamide (AEA; panel **a**), oleoylethanolamine (OEA; panel **b**), and palmitoylethanolamide (PEA;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

https://doi.org/10.1186/s13229-019-0256-6. Open Access under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

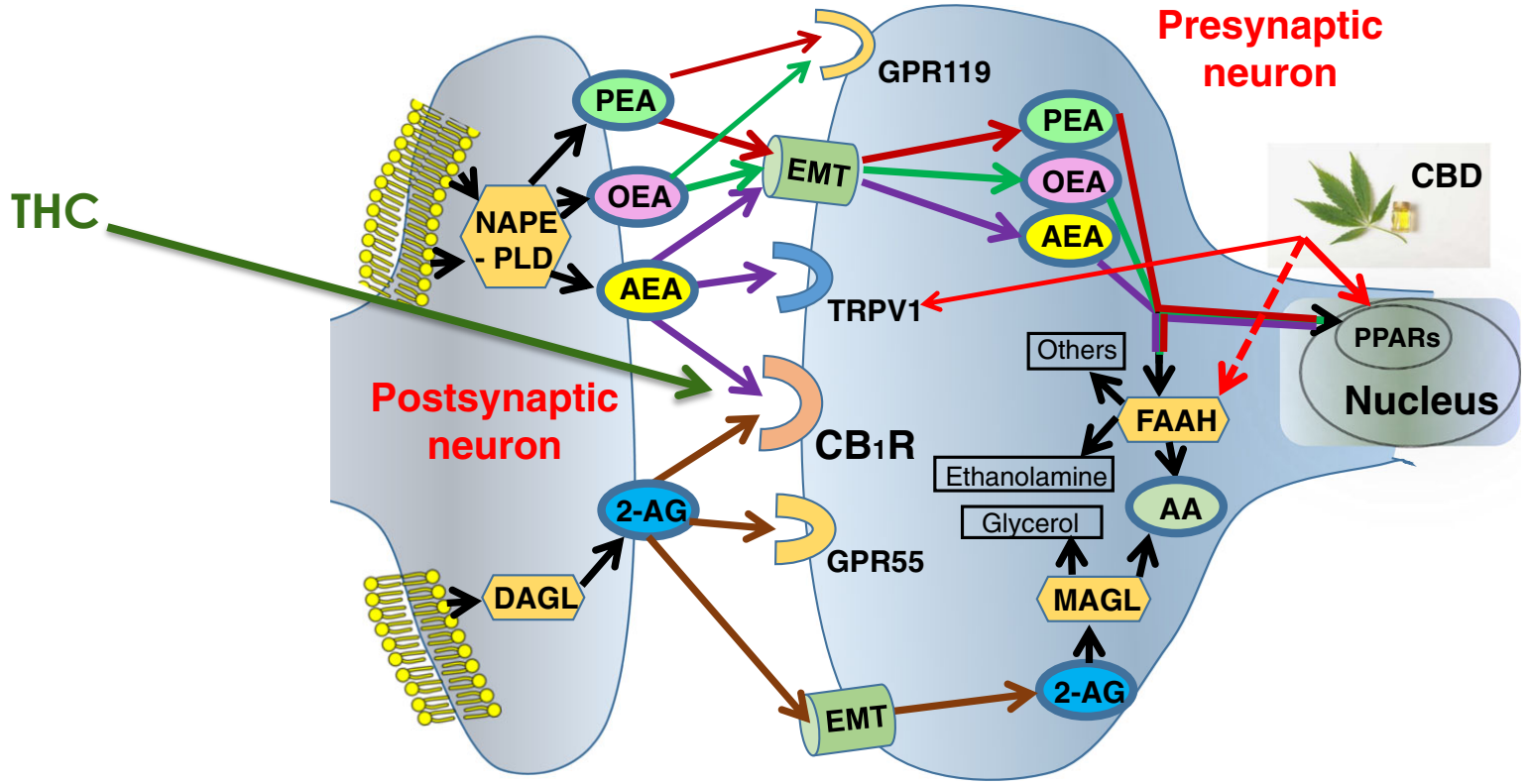


Fig. 5 Schematic diagram of the endocannabinoid system, relevant to this study. Legend: biosynthesis, degradation, and receptors' binding of AEA, 2-AG, OEA, and PEA are presented. AEA, PEA, and OEA are synthesized from the membrane's phospholipids by *N*-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD). PEA and OEA do not bind CB_1R, but they can enhance *AEA* activity at transient receptor potential channels of vanilloid type-1 (TRPV1). AEA, PEA, and OEA are all degraded by fatty acid amide hydrolase (FAAH) and hence OEA and PEA can increase AEA levels by competing with AEA for FAAH (mainly OEA) or by downregulating FAAH expression (mainly PEA). Cannabidiol (CBD), a non-psychoactive component of the cannabis plant, activates peroxisome proliferator-activated receptors (PPARs) and TPRV1 and inhibits FAAH and hence might compensate for lower levels of AEA, OEA, and PEA in children with ASD. DAGL, diacylglycerol lipase; MAGL, monoacylglycerol lipase. EMT, endocannabinoid membrane transporter; GPR55, G protein-coupled receptor 55

https://doi.org/10.1186/s13229-019-0256-6. Open Access under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

Case Study: Dronabinol

- 6-year old
- THC total d
  - 2 drops in
- Aberrant B
  - hyperact
  - lethargy
  - irritability
  - stereotyp
  - inapprop
- No adverse

e evening.

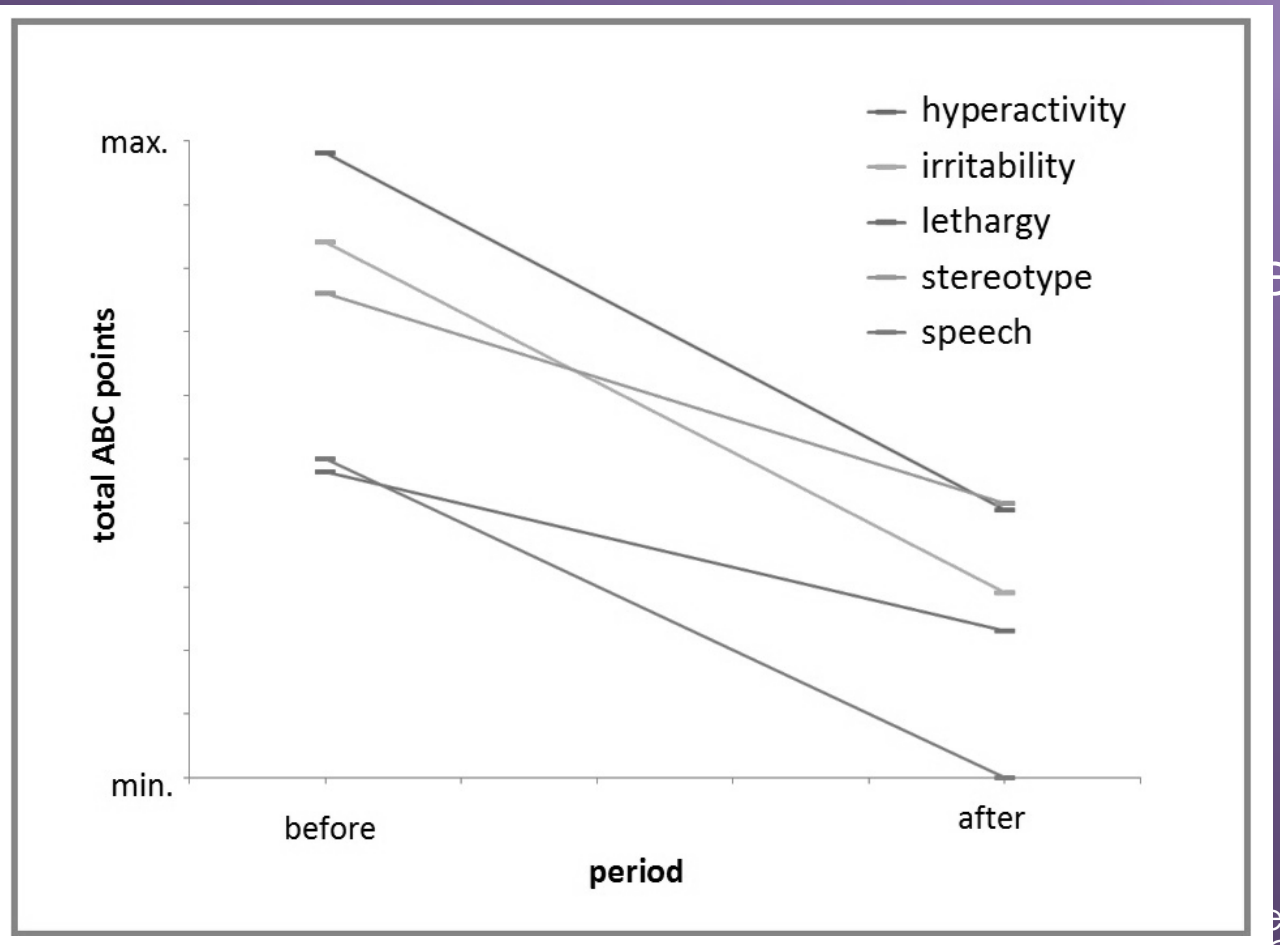


Figure 1. Change of ABC subscales within six months.

Kurz, René, and Kurt Bla

e-study with an early infantile
Cannabinoids 5.4 (2010): 4-6.

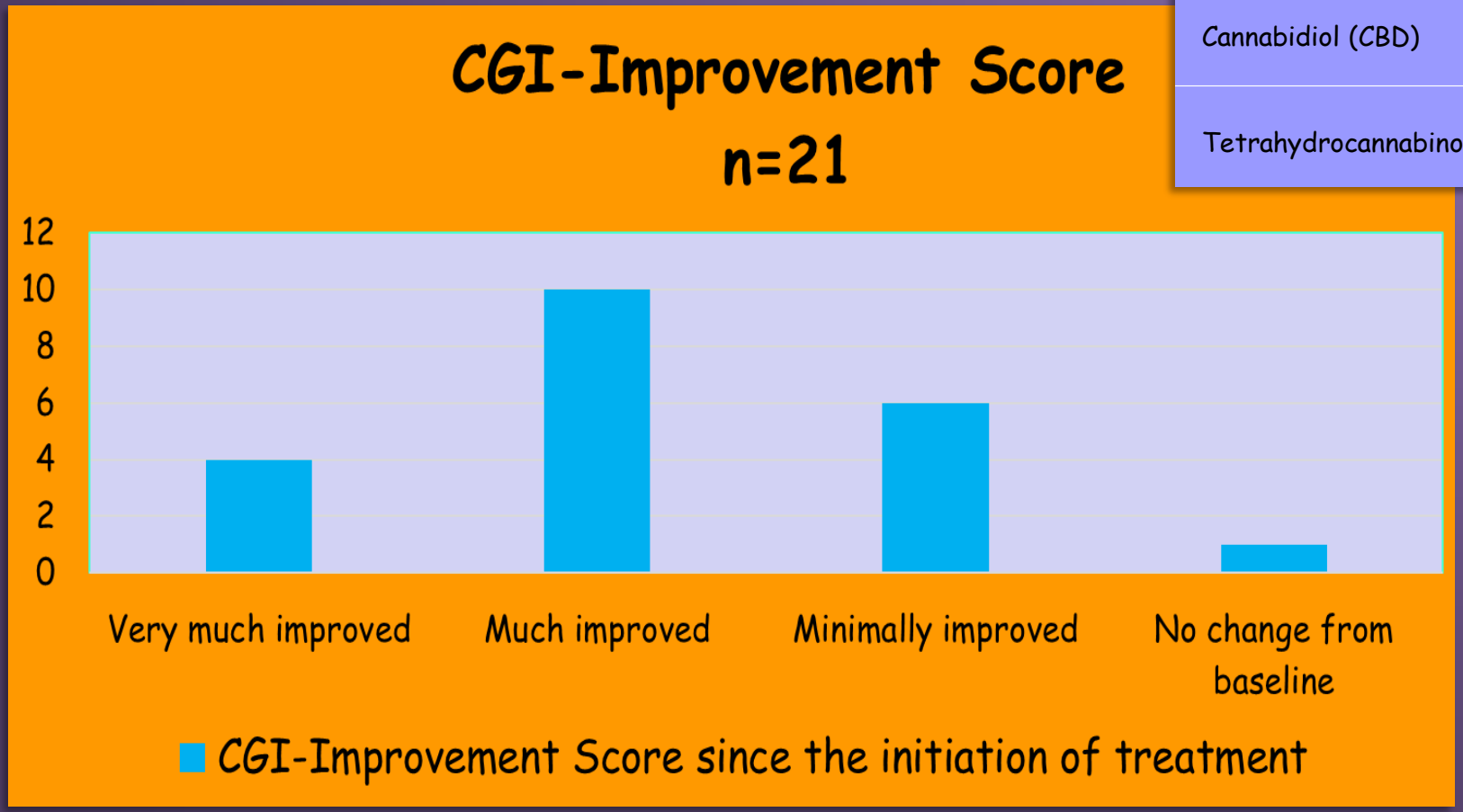
Observational Data from Chile

- 20 children & 1 adult with ASD, roughly equal distribution of the three severity levels.
  - Two thirds unsuccessfully treated with risperidone, aripiprazole, quetiapine and/or methylphenidate.
- 71% received balanced CBD:THC extracts
- 19.0% CBD-dominant extracts
- 9.5% THC-dominant extracts
- Mean follow up 7.6 months

Kuester, G., et al. "Oral cannabis extracts as a promising treatment for the core symptoms of autism spectrum disorder: preliminary experience in chilean patients." *Journal of the Neurological Sciences* 381 (2017): 932-933.

Observational Data from Chile

Type of cannabinoid	Range of administered dose	Mean administered dose
Cannabidiol (CBD)	0.17 - 13.32 mg/day	1.94 mg/day
Tetrahydrocannabinol (THC)	0.22 - 5.26 mg/day	0.89 mg/day



CBD:THC ratio	
Range	2.53 - 0.45
Mean	1.66

Kuester, G., et al. "Oral cannabis extracts as a promising treatment for the core symptoms of autism spectrum disorder: preliminary experience in chilean patients." *Journal of the Neurological Sciences* 381 (2017): 932-933.

Journal of Autism and Developmental Disorders
https://doi.org/10.1007/s10803-018-3808-2

BRIEF REPORT

Published online: 31 October 2018

Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems—A Retrospective Feasibility Study

Adi Aran[1] · Hanoch Cassuto[2] · Asael Lubotzky[1] · Nadia Wattad[1] · Esther Hazan[1]

- Observational study of CBD-rich oil in 60 children with ASD and severe behavioral problems
  - 77% low functioning, 83% boys
- Administered sublingually 2-3x/day
  - up-titrated over 2–4 weeks to effect and tolerability
  - starting dose 1 mg/kg/day, max dose10 mg/kg/day
  - 7 to 13 months of treatment

Journal of Autism and Developmental Disorders
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BRIEF REPORT

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- 61% of patients had significant improvement in behavior problems
  - much improved or very much improved on CGI scale
- Following the cannabis treatment:
  - 16 (33%) received fewer medications or lower dosage
  - 12 (24%) stopped taking medications
  - 4 (8%) received more medications or higher dose

Journal of Autism and Developmental Disorders
https://doi.org/10.1007/s10803-018-3808-2

BRIEF REPORT

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Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems—A Retrospective Feasibility Study

Adi Aran[1] · Hanoch Cassuto[2] · Asael Lubotzky[1] · Nadia Wattad[1] · Esther Hazan[1]

- In 29 patients with an insufficient response to the original 20:1 formulation, lower CBD:THC ratios were used (up to a 6:1).
- Lower CBD:THC ratio reported to be much better in 13 patients, slightly better in 7 patients, no change in 6 and worse in 3.

Table 1 Adverse events reported by parents during the treatment with cannabis

Adverse event	No of patients (%)
Any adverse event	29 (51%)
Sleep disturbances	8 (14%)
Restlessness	5 (9%)
Nervousness	5 (9%)
Loss of appetite	5 (9%)
Gastrointestinal symptoms	4 (7%)
Unexplained laugh	4 (7%)
Mood changes	3 (5%)
Fatigue	3 (5%)
Nocturnal enuresis	2 (3.5%)
Gain of appetite	2 (3.5%)
Weight loss	2 (3.5%)
Weight gain	2 (3.5%)
Dry mouth	2 (3.5%)
Tremor	2 (3.5%)
Sleepiness	1 (2%)
Anxiety	1 (2%)
Confusion	1 (2%)
Cough	1 (2%)
Serious adverse event	**No of patients (%)**
Psychotic event	1 (2%)

One girl who used a lower CBD:THC ratio (max THC dose 0.72 mg/kg/day) had a transient serious psychotic event which required treatment with an antipsychotic.

Aran, Adi, et al. "Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems—A Retrospective Feasibility Study." *Journal of autism and developmental disorders* 49.3 (2019): 1284-1288.

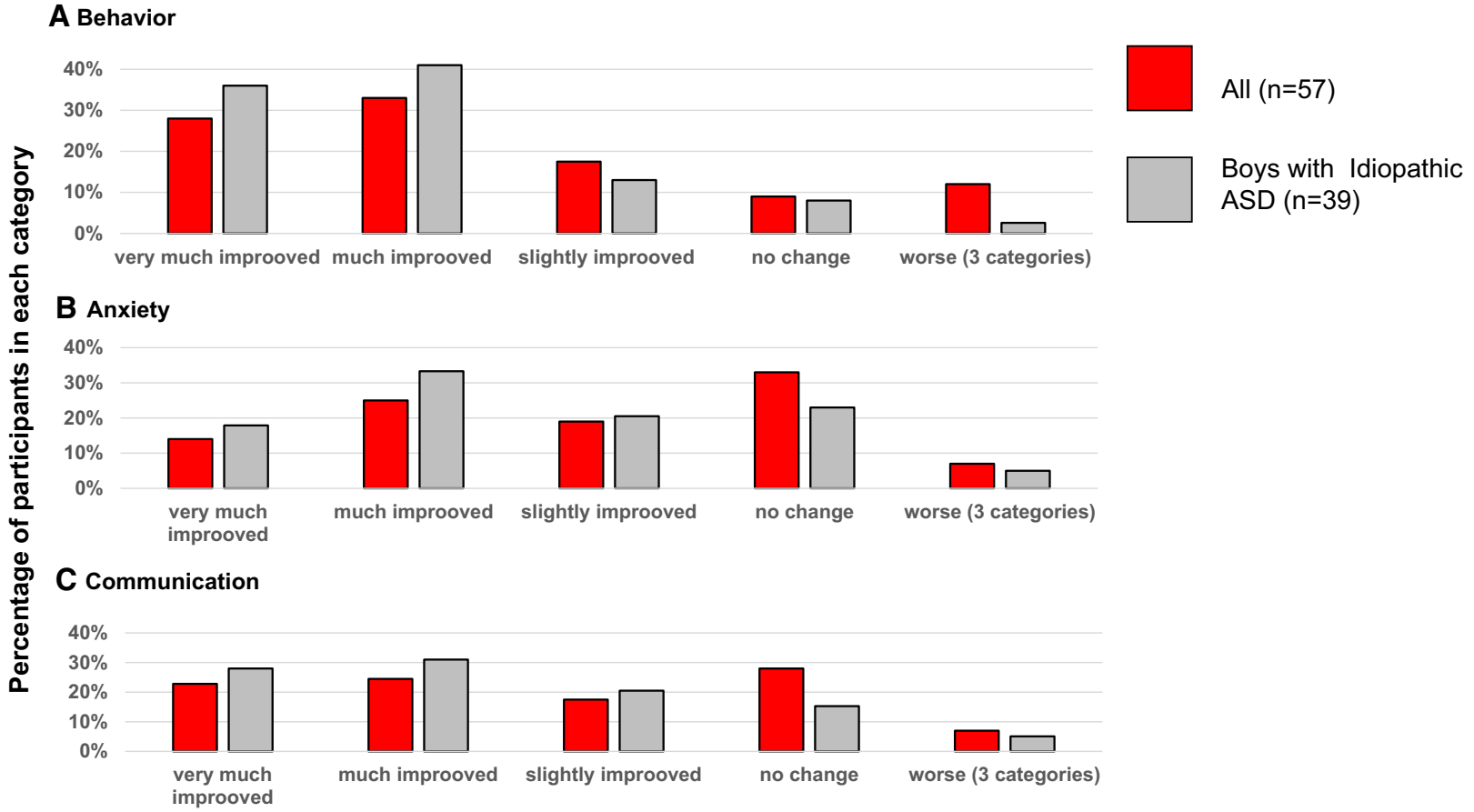

Fig. 1 Caregivers global impression of change in behavior anxiety and communication following cannabis treatment

Aran, Adi, et al. "Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems—A Retrospective Feasibility Study." *Journal of autism and developmental disorders* 49.3 (2019): 1284-1288.

Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy

Lihi Bar-Lev Schleider[1,2], Raphael Mechoulam[3], Naama Saban[2], Gal Meiri[4,5] & Victor Novack[1]

SCIENTIFIC REPORTS | (2019) 9:200 | DOI:10.1038/s41598-018-37570-y

- Observational study with 188 patients
  - 90% with restlessness
  - 80% with rage attacks
  - 79% with agitation.
- Primarily treated with CBD:THC 20:1 oil, with an average dose of 79.5 ± 61.5 mg CBD and 4.0 ± 3.0 mg THC given TID.
- Insomnia in 46 patients (24.4%) was treated with an evening does of THC oil, average 5.0 ± 4.5 mg THC daily

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SCIENTIFIC REPORTS | (2019) 9:200 | DOI:10.1038/s41598-018-37570-y

- 30% reported a significant improvement
- 54% moderate improvement
- 7% slight improvement
- 9% had no change

- Of the 55 patients taking antipsychotics, 11 discontinued them and 3 reduced the dose.

Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy

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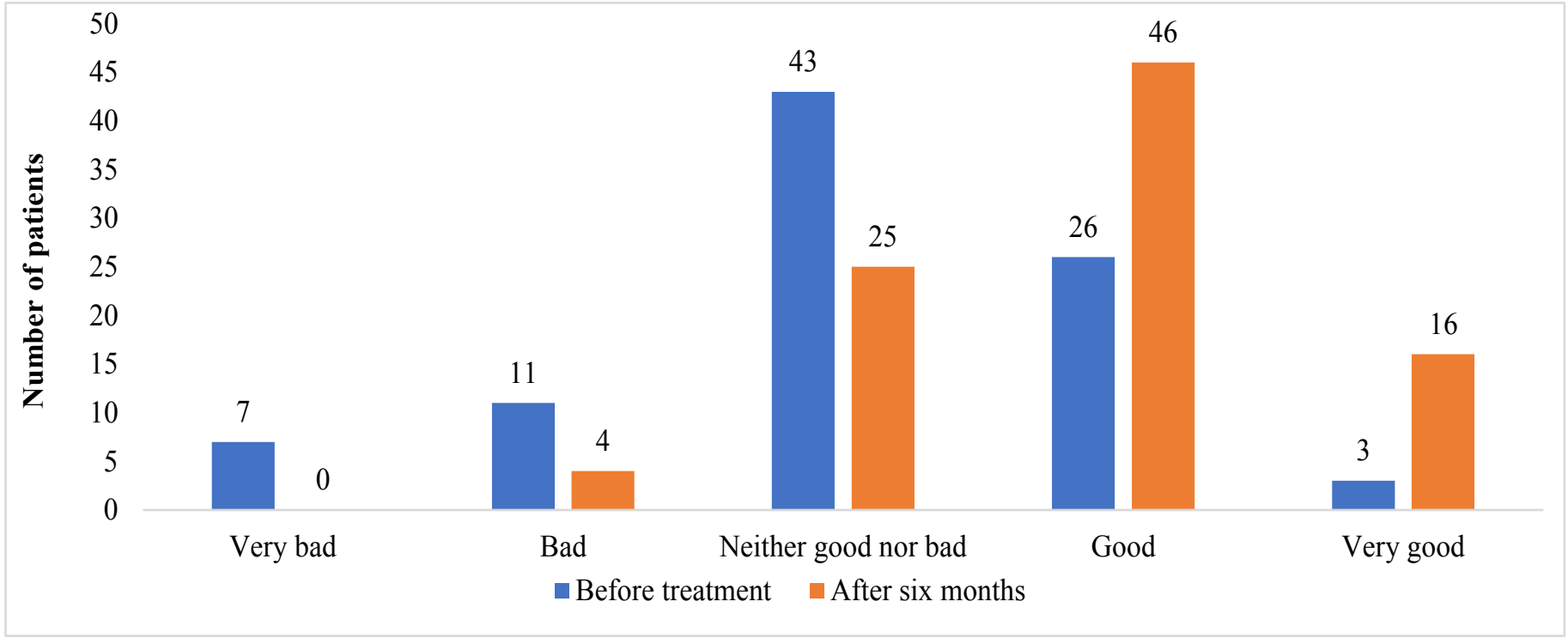
SCIENTIFIC REPORTS | (2019) 9:200 | DOI:10.1038/s41598-018-37570-y

Supplementary figure S2: Quality of life assessment. Quality of life was assessed prior to and six months after initiation of cannabis treatment. $p<0.001$



Oral Cannabidiol Use in Children With Autism Spectrum Disorder to Treat Related Symptoms and Co-morbidities

Dana Barchel[1†], Orit Stolar[2†], Tal De-Haan[1], Tomer Ziv-Baran[3], Naama Saban[4], Danny Or Fuchs[1], Gideon Koren[1,5] and Matitiahu Berkovitch[1]*

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 09 January 2019
doi: 10.3389/fphar.2018.01521

- 53 children w/ ASD
  - median age of 11 (4–22) years
  - median Tx duration 66 days (30–588).
- 20:1 CBD-rich oil up to 16 mg/kg CBD and 0.8 mg/kg THC

Oral Cannabidiol Use in Children With Autism Spectrum Disorder to Treat Related Symptoms and Co-morbidities

Dana Barchel[1†], Orit Stolar[2†], Tal De-Haan[1], Tomer Ziv-Baran[3], Naama Saban[4], Danny Or Fuchs[1], Gideon Koren[1,5] and Matitiahu Berkovitch[1]*

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 09 January 2019
doi: 10.3389/fphar.2018.01521

- Self-injury and rage attacks (*n* = 34)
  - improved in 67.6%
  - worsened in 8.8%.
- Hyperactivity (*n* = 38)
  - improved in 68.4%
  - no change in 28.9%
  - worsened in 2.6%.
- Sleep problems (*n* = 21)
  - improved in 71.4%
  - worsened in 4.7%.
- Anxiety (*n* = 17)
  - improved in 47.1%
  - worsened in 23.5%.

Oral Cannabidiol Use in Children With Autism Spectrum Disorder to Treat Related Symptoms and Co-morbidities

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frontiers in Pharmacology

ORIGINAL RESEARCH
published: 09 January 2019
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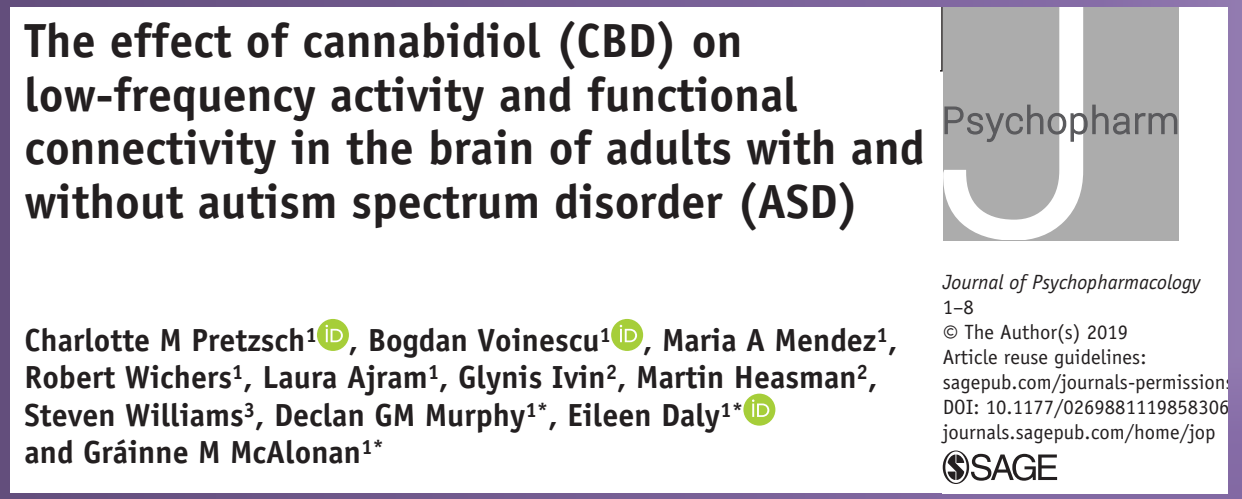
Distinct from the two previous cohorts, the most common adverse event was somnolence (23%) followed by decreased appetite (11%).



The effect of cannabidiol (CBD) on low-frequency activity and functional connectivity in the brain of adults with and without autism spectrum disorder (ASD)

Charlotte M Pretzsch[1], Bogdan Voinescu[1], Maria A Mendez[1], Robert Wichers[1], Laura Ajram[1], Glynis Ivin[2], Martin Heasman[2], Steven Williams[3], Declan GM Murphy[1*], Eileen Daly[1*] and Gráinne M McAlonan[1*]

Psychopharm

Journal of Psychopharmacology
1–8
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DOI: 10.1177/0269881119858306
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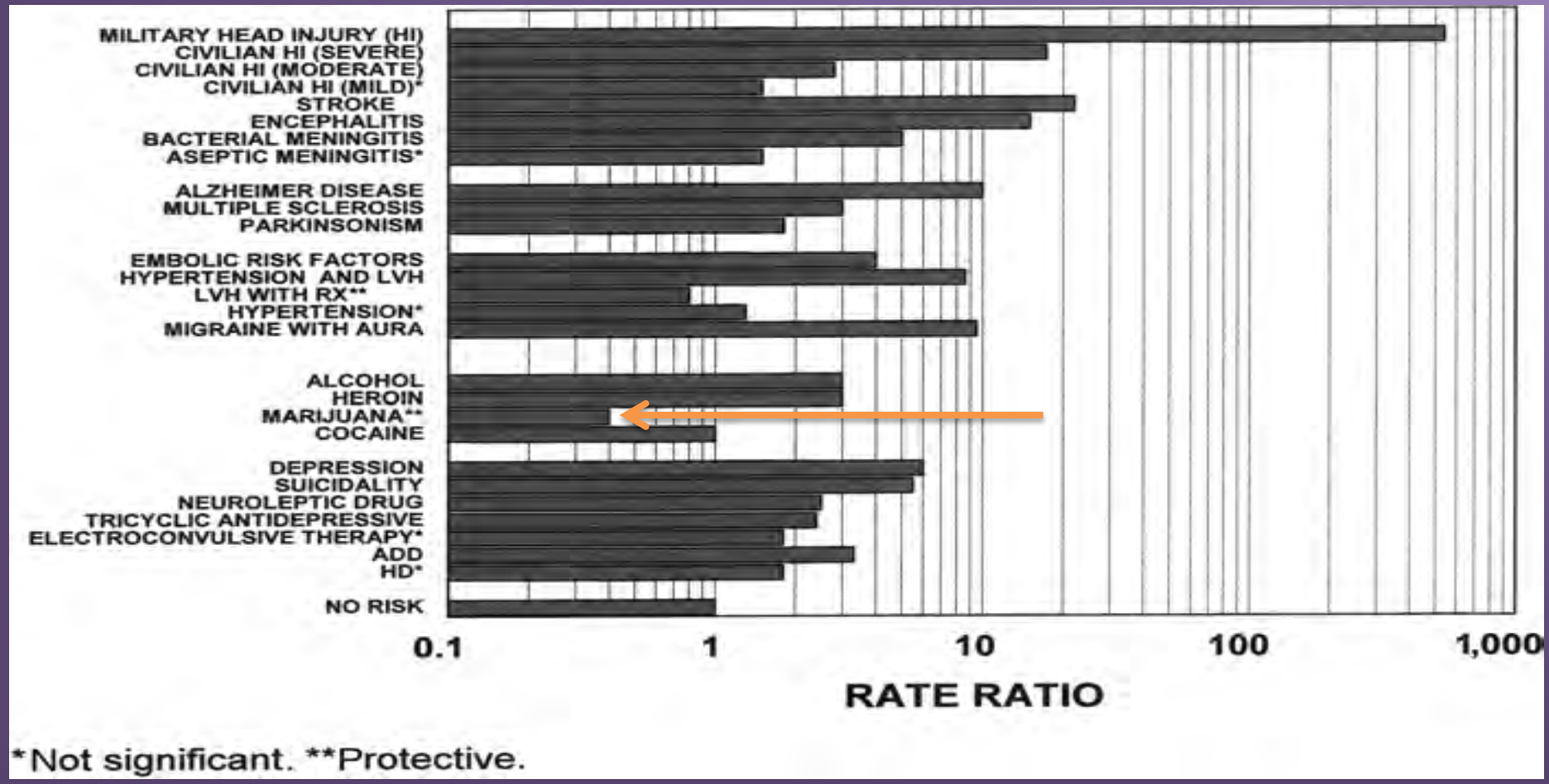
SAGE

- fMRI study of 34 healthy men (half with ASD), CBD 600mg or placebo
- In the ASD group, but not the neurotypical group, CBD significantly:
  - increased low-frequency fluctuations in the cerebellar vermis and the right fusiform gyrus
  - altered vermal functional connectivity with several of its subcortical (striatal) and cortical targets

Cannabis in Epilepsy

Marijuana Use Protective Against Epilepsy



Banerjee, POONAM NINA, and W. ALLEN Hauser. "Incidence and prevalence." *Epilepsy: a comprehensive textbook* 1 (2008): 45-56.

Four Millennia of Historical Evidence

- Ancient Sumerian and Akkadian tablets reference the use of a medicinal plant that is most likely cannabis for a host of ailments including nocturnal convulsions around 1800 BCE
- Specific mentions of the treatment of epilepsy are found in the 11th century writings of the Arabic physician al-Mayusi who advocated the use of leaf juice of cannabis through the nose.
- O'Shaughnessy reports treating infantile convulsions in 1840.
- Prominent neurologist Sir William Gowers describes treatment of seizures w/ cannabis in 1881.

Reviewed in Friedman & Sirven, 2017& in Russo 2017

“Because of the therapeutic failures and because of the toxicity associated with the currently used antiepileptics, the search for relatively non-toxic drugs with different mechanisms of action is an obvious goal in epilepsy research. Both the lack of toxicity and the anticonvulsant properties of CBD combine to enhance its therapeutic potential as an antiepileptic.”

What year would you guess this observation was made?

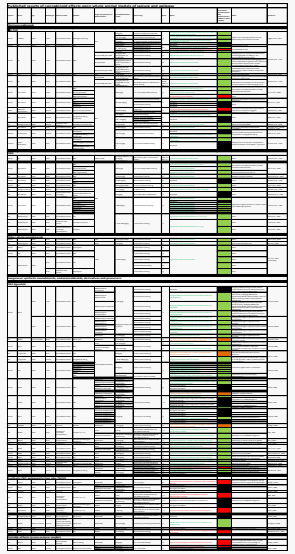
Karler, R., and S. A. Turkanis. 1979. "Cannabis and epilepsy." In *Marihuana biological effects: Analysis, metabolism, cellular responses, reproduction and brain.*, edited by G. G. Nahas and W. D. M. Paton, 619-641. Oxford, UK: Pergamon Press.

CINN Centre for Integrative Neuroscience and Neurodynamics

University of Reading

Summary of preclinical evidence

- Large preclinical evidence base asserting anticonvulsant effects.
- Summary findings, full monograph and all citations freely available as PDF on request



Compound	Species	Number of discrete conditions/models/designs	Dose	Anticonvulsant	No effect	Proconvulsant
THC	6	31	0.25-200 mg/kg	61%	29%	10%*
CBD	2	21	1-400 mg/kg	81%	19%	0%
Other plant cannabinoids	2	7	N/A	100%	0%	0%
CB1 receptor agonists	2	55	N/A	73%	18%	2% (7% mixed effect)

*Includes non-seizure studies where convulsions were reported (see next slide)

Slide courtesy of Dr. Benjamin J. Whalley

ECS Dysregulation in Epilepsy

- 30 hippocampal samples were obtained from patients with therapy-resistant temporal lobe epilepsy who had temporal lobectomy, compared to 11 controls
- CB1 mRNA was downregulated to 1/3 its control value in epileptic hippocampus (qPCR measurements).
- Expression of diacylglycerol lipase (enzyme responsible for 2-AG synthesis) was reduced by 60%.
- CB1 immunolabeling was decreased in epileptic hippocampus
  - No changes in the ratio of CB1-positive GABAergic boutons
  - Robust reduction in the fraction of CB1-positive glutamatergic axon terminals

Ludanyi et al, 2008

ECS Dysregulation in Epilepsy

"These findings show that a neuroprotective machinery involving endocannabinoids is impaired in epileptic human hippocampus and imply that downregulation of CB1 receptors and related molecular components of the endocannabinoid system may facilitate the deleterious effects of increased network excitability."

Ludanyi et al, 2008

Report Of A Parent Survey Of Cannabidiol-enriched Cannabis Use In Pediatric Treatment-resistant Epilepsy

- Solicited data from an online Facebook survey of 150 families whose children were using CBD-enriched cannabis to treat drug resistant seizures
- 19 responses (12.7%): 13 Dravet syndrome, 4 Doose syndrome, 1 Lennox-Gastaut syndrome, 1 idiopathic epilepsy
- Average previois Rx of of 12 AEDs

Porter & Jacobson, 2013

- Overall, 84% noted decreased seizure frequency on CBD:
  - 2 (11%) had complete remission
  - 8 (42%) had >80% reduction in seizure frequency
  - 6 (32%) had 25-60% reduction

- Cannabidiol was associated with adverse events:
  - Drowsiness: 37%
  - Fatigue: 16%

- With some side benefits:
  - Better mood: 79%
  - Increased alertness: 74%
  - Better sleep: 68%

- Study Limitations:
  - A preliminary survey of limited duration
  - A self-selected population with low response rate
  - No control group

Porter & Jacobson, 2013

Table 2
Epilepsy characteristics and response rate.

Seizure type	N	Responders	% Responders
Generalized tonic–clonic	30	9	30%
Focal	21	8	38%
Absence	18	5	28%
Myoclonic	15	3	20%
Epileptic spasms	14	5	36%
Tonic	12	2	17%
Atonic	9	4	44%
Syndrome type	**N**	**Responders**	**% Responders**
Doose syndrome	3	0	0%
Dravet syndrome	13	3	23%
Lennox–Gastaut syndrome	9	8	89%*

Responders reported >50% decrease in seizures.
* $p < 0.05$ Fisher's exact.

Table 3
OCE type and response.

OCE type	N	Responders
CBD only	52	18 (35%)
CBD + other OCE	8	5 (63%)
THCA only	5	0 (0%)
Other	10	2 (20%)

CBD = Cannabidiol, THCA = Tetrahydrocannabinolic acid.

Table 4
Reported improvements.

Additional improvements (56% of all patients)	Frequency	Percent
Alertness/behavior	25	33%
Language	8	11%
Motor skills	8	11%
Sleep	5	7%

Press CA, et al. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy & behavior.* 2015;45:49-52.

75 pts. in Colorado identified using cannabis extracts for intractable seizures.

57% reported improvement; 33% a >50% improvement

There was no difference in response rates by seizure type.

There was no difference in response rate of CBD strains vs. mixed strains, but no improvement in 5 pts. receiving THCA only

Response rate for families moving to CO was 47% vs. only 22% for those already there, and 3X as great for those reporting >50% response!

Improvements also noted in functional status

Contents lists available at ScienceDirect

Seizure

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

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

Michal Tzadok [a,1,*], Shimrit Uliel-Siboni [b,1], Ilan Linder [c], Uri Kramer [b], Orna Epstein [d], Shay Menascu [b], Andrea Nissenkorn [a], Omer Bar Yosef [a], Eli Hyman [d], Dorit Granot [e], Michael Dor [f], Tali Lerman-Sagie [c], Bruria Ben-Zeev [a]

- CBD dosage ranged from 1 to 20 mg/kg/d,
- Divided into two groups: 1–10 mg/kg/d & 10–20 mg/kg/d.
- Final dose used for each patient was defined according to seizure response and side effects.
- The THC dosage did not exceed 0.5 mg/ kg/d

Table 2
Seizure reduction according to dosage.

Dosage	0% no. of cases	<25% no. of cases	25–50% no. of cases	50–75% no. of cases	>75% no. of cases	Total no. of cases
<10 mg/kg/d	4	14	8	24	10	60 (81%)
>10 mg/kg/d	4	5	1	1	3	14 (19%)

Table 3
Adverse events reported in 34/74 patients.

Adverse events	No. of cases
Seizure aggravation	13 (18%)
Somnolence/fatigue	16 (22%)
Gastrointestinal problems and irritability	5 (7%)

Devinsky O, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol.* 2016;15(3):270-8.

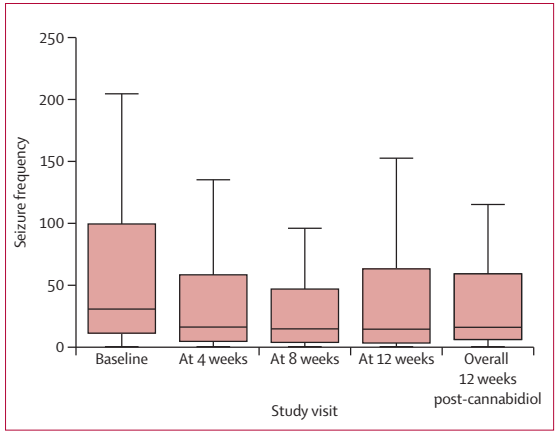


***Figure 2*: Monthly frequency of motor seizures in patients in the efficacy analysis group (n=137)**
Boxplots show median values, with 25th and 75th percentiles. The whiskers denote the 25th percentile – 1·5 × IQR and the 75th percentile + 1·5 × IQR.

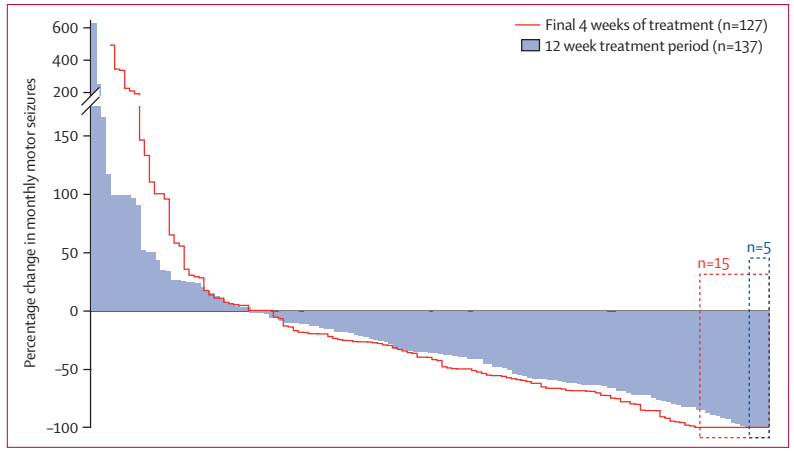
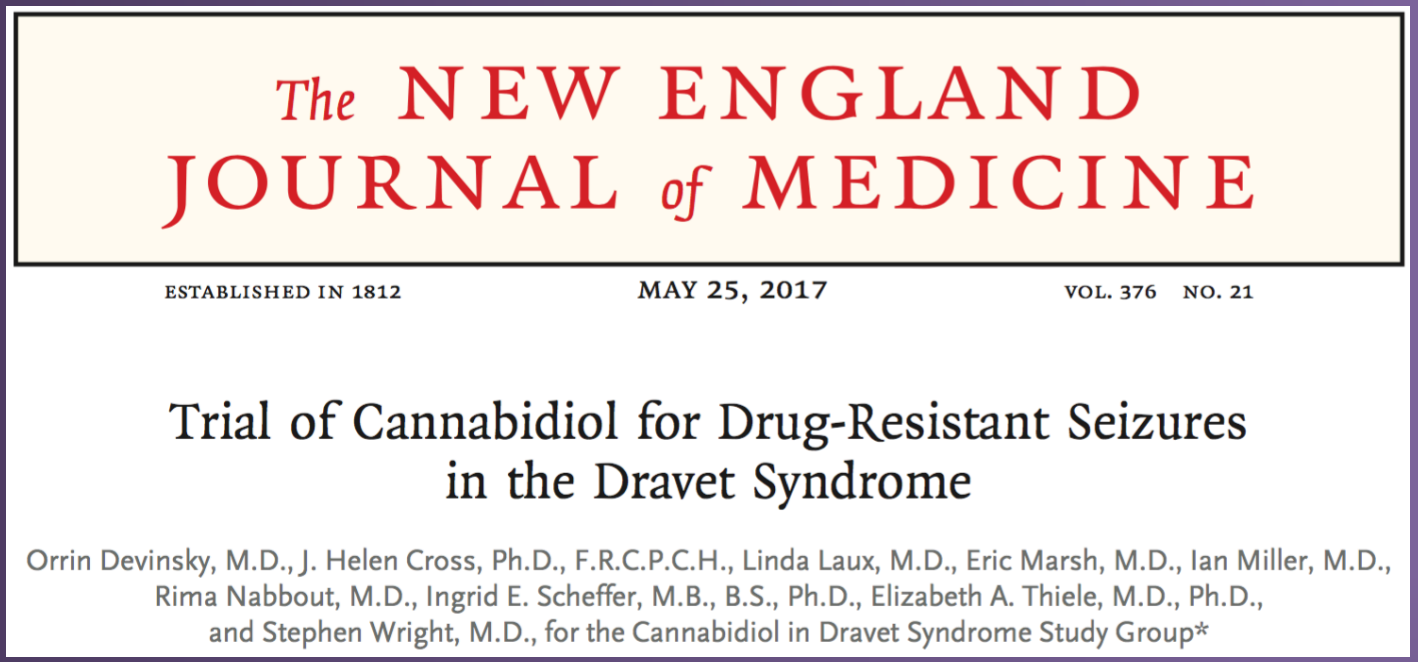


***Figure 3*: Percentage change in monthly frequency of motor seizures in patients in the efficacy analysis group (n=137)**
Percentage changes for each patient are ordered from greatest increase to greatest decrease. The dashed boxes indicate patients who became free of that seizure type during the 12 week treatment period (blue) or the last 4 weeks of treatment (red).

- 162/214 pts. observed over 12 w., starting CBD 2-5 mg/kg/d titrating to 25-50 (mean dose 22.7-22.9 mg/kg/d)
- AE: somnolence 25%, decreased appetite 19%, diarrhea 19%. Only 3% discontinued due to AEs.
- Sedation prominent with Clobazam
- Median change in total seizures was -34.6%, greatest with focal sz. (-55%)
- 39% had >50% reduction in motor spells, 21% had >70% reduction, 9% >90% reduction. Effective for Dravet and Lennox-Gastaut syndromes.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 25, 2017 VOL. 376 NO. 21

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

- Double-blind placebo-controlled, n=120 age 2-18
- Patients had previously tried a median of 4.0 antiepileptic drugs (range 0-26) and were taking median of 3.
- CBD 20mg/kg for 14 weeks.
- Median frequency of monthly convulsive seizures decreased from 12.4 to 5.9 with cannabidiol
  - 14.9 to 14.1 with placebo
- No significant reduction in nonconvulsive seizures .

- Adverse events that occurred more frequently in the cannabidiol group than in the placebo group: diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests
- No negative effect of cannabidiol on sleep
- Quality of Life in Childhood Epilepsy and Vineland-II scores showed no significant difference between cannabidiol and placebo
- Elevated aminotransferase levels occurred in 12 patients in the cannabidiol group and 1 in the placebo group, all inpatients taking valproate

Lattanzi, Simona, et al. "Efficacy and safety of cannabidiol in epilepsy: a systematic review and meta-analysis." *Drugs* 78.17 (2018): 1791-1804.

- Meta-analysis of four RCTs (n=550)
- Average improvement in seizure frequency with CBD 10 and 20 mg/kg/d, compared with placebo, was 19.5% (P = 0.001) and 19.9% (P < 0.001) respectively.
- 50% reduction in all seizure types occurred in 37.2% of patients receiving 20 mg/kg/d and 21.2% of patients receiving placebo
  - statistically significant, but demonstrates the high placebo effect associated with subjective (usually parent-reported) outcomes

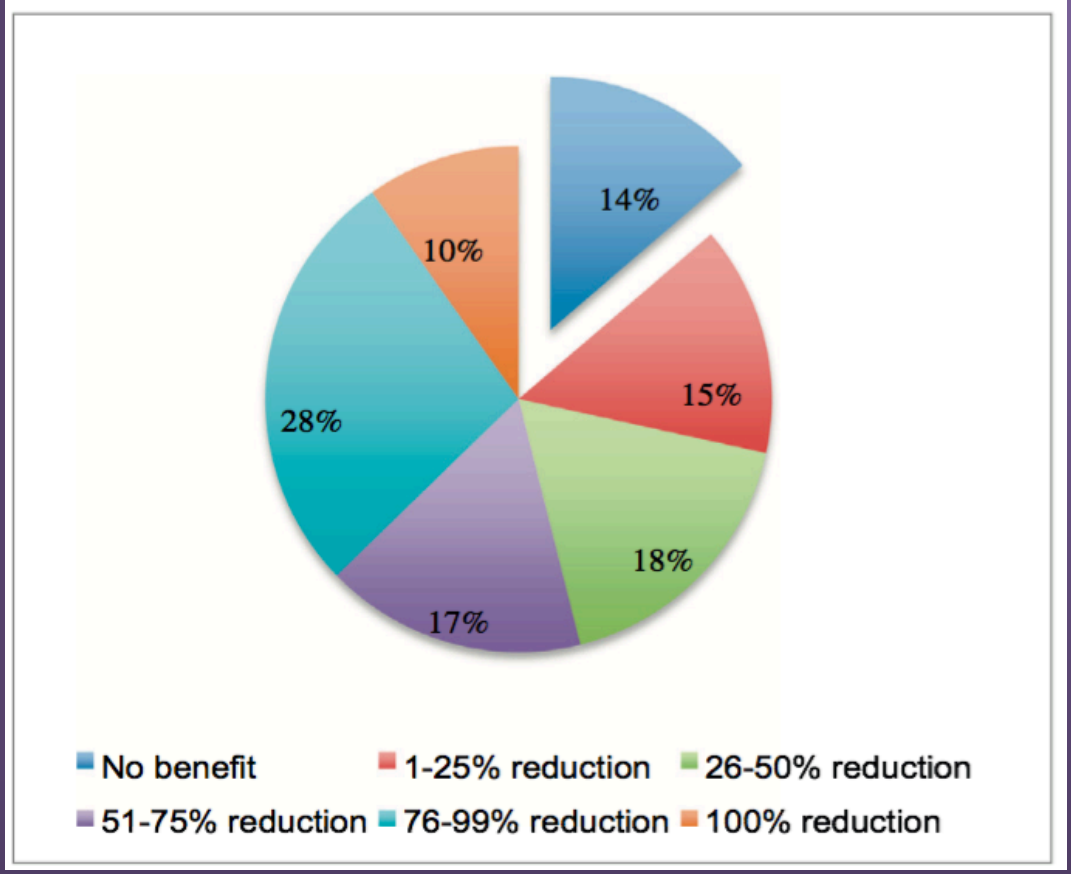
Contents lists available at ScienceDirect

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]



- n=272 patients w/ refractory epilepsy
- Effective total cannabinoid doses: 0.05 - 9 mg/kg/day, primarily CBD
- Effective serum levels of CBD: 1.8 - 80 ng/mL
- Case reports:
  - THCA preventing seizures
  - THC aborting GTC

Cannabis Seizure Rescue Formula

- THC 3-30mg per dose
- Administered prior to benzodiazepines
- Rubbed into gums or PR
- Abort seizures, speed recovery, prevent clusters

Neurological Sciences
https://doi.org/10.1007/s10072-019-04162-1

BRIEF COMMUNICATION

The use of medical grade cannabis in Italy for drug-resistant epilepsy: a case series

Chiara Pane[1] · Francesco Saccà[1]

Received: 11 July 2019 / Accepted: 15 November 2019
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Table 2 Patients seizure types, cannabis therapy, and percent seizure reduction

Case	Epilepsy type	Previous AEDs	Current AEDs	Comorbidity	Effective cannabis product	Effective dose	Baseline monthly seizure frequency	Seizure reduction	Follow-up
1	Non-specific epileptic encephalopathy 21 year-old	VPA (800 mg), CBZ (500 mg), LMT (75 mg), TPX (100 mg), LTC (250 mg), ZNS (200 mg)	VPA 400 mg BID ZNS 100 mg BID CBZ 250 mg BID	-Central diabetes insipidus -Congenital central hypothyroidism -Splenic hamartomas	Bedrocan-OOE	18 mg THC 1 mg CBD	20 GTCs	60%	4 months
2	West syndrome 18 year-old	CS (NA), PB (60 mg), VPA (800 mg), TPX (300 mg), LTC (3200 mg), KET.	TPX 150 mg BID LTC 1600 mg BID VPA 400 mg BID	Nothing to report	Bedrocan-OOE	12 mg THC 0.7 mg CBD	600 GTCs	80%	48 months
3	Polymicrogyria-associated epilepsy 15 year-old	VPA (400 mg), PB (60 mg), TPX (200 mg), LTC (1500 mg), CBZ (500 mg), LMT (125 mg).	LTC 750 mg BID LCS 100 mg BID TPX 100 mg BID	Nothing to report	Bedrolite-OOE	0.8 mg THC 7.2 mg CBD	10 GTCs	80%	12 months
4	Genetic epilepsy with CACNA 1a mutation 4 year-old	VPA (600 mg), CBZ (240 mg), CB (2,5 mg), PB (45 mg), SP (NA), ACZ (NA)	CBZ 80 mg TID VPA 200 mg TID	Patent ductus arteriosus	Bedrolite-OOE	0.5 mg THC 4.7 mg CBD	210 Abs +1.5 GTC	75%	14 months
5	Juvenile absence epilepsy 25 year-old	PB (NA), LTC (3000 mg), CBZ (800 mg), LMT (200 mg), TPX (200 mg), VPA (1000 mg), LCM (400 mg)	LTC 1000 mg BID TPX 200 mg BID	Ovarian cyst	Bedrocan_OOE	12 mg THC 0.7 mg CBD	600Abs + 2 GTCs/year	95%	12 months

Previous AED refers to all AEDs used in the past, current AED refers to the AED combination on the day we started cannabis

VPA, valproic acid; *CBZ*, carbamazepine; *LMT*, lamotrigine; *TPX*, topiramate; *LTC*, levetiracetam; *KET*, kethogenic diet [12]; *ZNS*, zonesamide; *CS*, corticosteroids; *PB*, phenobarital; *SP*, stiripentol; *ACZ*, acetazolamide; *LCM*, lacosamide; *CB*, clobazam; *NA*, not available; *THC*, tetrahydrocannabinol; *CDB*, cannabidiol; *OOE*, olive oil extract; *Abs*, absence; *GTC*, generalized tonic-clonic seizure; *AED*, anti-epileptic drug; *BIS*, bis in die; *TID*, ter in die

Neurological Sciences
https://doi.org/10.1007/s10072-019-04162-1

BRIEF COMMUNICATION

Check for updates

The use of medical grade cannabis in Italy for drug-resistant epilepsy: a case series

Chiara Pane[1] · Francesco Saccà[1]

Received: 11 July 2019 / Accepted: 15 November 2019
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- Case 2: improved quality and duration of sleep, social interaction, and reduced spasticity
- Case 3: Alertness improved, as did sleep and mood
- Case 4: Parents reported quality and duration of sleep and a psychomotor improvement
- Case 5: one episode of panic attack

Potential Clinical Benefits of CBD-Rich *Cannabis* Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis

Fabricio A. Pamplona[1], Lorenzo Rolim da Silva[2] and Ana Carolina Coan[3]*

[1] *Entourage Phytolab, São Paulo, Brazil,* [2] *Bedrocan Brasil, São Paulo, Brazil,* [3] *UNICAMP, Campinas, Brazil*

frontiers in Neurology

SYSTEMATIC REVIEW
published: 12 September 2018
doi: 10.3389/fneur.2018.00759

- 11 papers through Dec 2017
- n=670 total (447 CBD-extract, 223 pure CBD)
- Strict inclusion criteria: objective measurements

	CBD-rich extract	Purified CBD
Reports of improvement p <0.0001	71%	36%
Reports of >50% seizure reduction p = 0.56	38%	42%
Average daily dose	6.1 mg/kg/day	27.1 mg/kg/day
Adverse events: Mild Severe p < 0.0001	 38% 8%	 84% 22%

Karler, R., and S. A. Turkanis. 1979. "Cannabis and epilepsy." In *Marihuana biological effects: Analysis, metabolism, cellular responses, reproduction and brain.*, edited by G. G. Nahas and W. D. M. Paton, 619-641. Oxford, UK: Pergamon Press, p. 624.

TABLE 1. ANTICONVULSANT ACTIVITY OF NATURALLY OCCURRING CANNABINOIDS AND DERIVATIVES IN THE MES TEST (MICE)

	ED_{50} or maximum dose* (mg/kg)	Anticonvulsant activity
CBD	120	+
Δ^9-THC	100	+
11-OH-Δ^9-THC	14	+
8α-OH-Δ^9-THC	100*	0
8β-OH-Δ^9-THC	100*	+
Δ^9-THC acid A	200*	+
Δ^9-THC acid B	400*	+
Δ^8-THC	80	+
9-nor-Δ^8-THC	100*	+
CBN	230	+
9-nor-9α-OH-hexahydro CBN	100*	+
9-nor-9β-OH-hexahydro CBN	100*	+
DMHP	13	+
d,l-threo-DMHP	7	+
d,l-erythro-DMHP	24	+
Cannabichromene	500*	0
Olivetol	500*	0

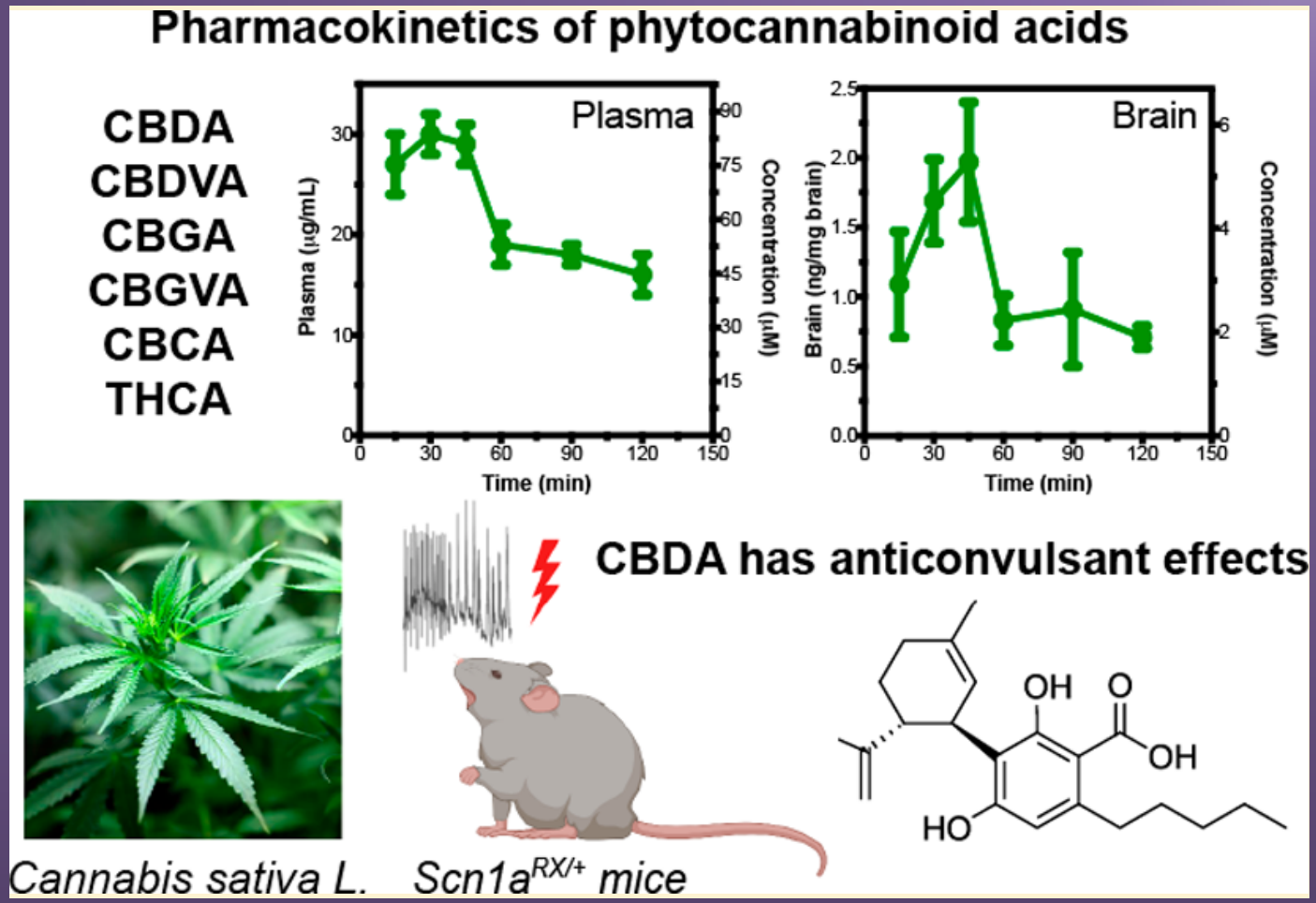
ED_{50} values were calculated from dose-response data; the starred (*) values represent an assessment of anticonvulsant activity in the absence of ED_{50} data based on the maximum dose tested.

JOURNAL OF NATURAL PRODUCTS

Pharmacokinetics of Phytocannabinoid Acids and Anticonvulsant Effect of Cannabidiolic Acid in a Mouse Model of Dravet Syndrome

Lyndsey L. Anderson,[†,‡] Ivan K. Low,[†] Samuel D. Banister,[†,§] Iain S. McGregor,[†,⊥] and Jonathon C. Arnold*[,†,‡]

[†]Lambert Initiative for Cannabinoid Therapeutics, Brain and Mind Centre, The University of Sydney, Sydney, New South Wales



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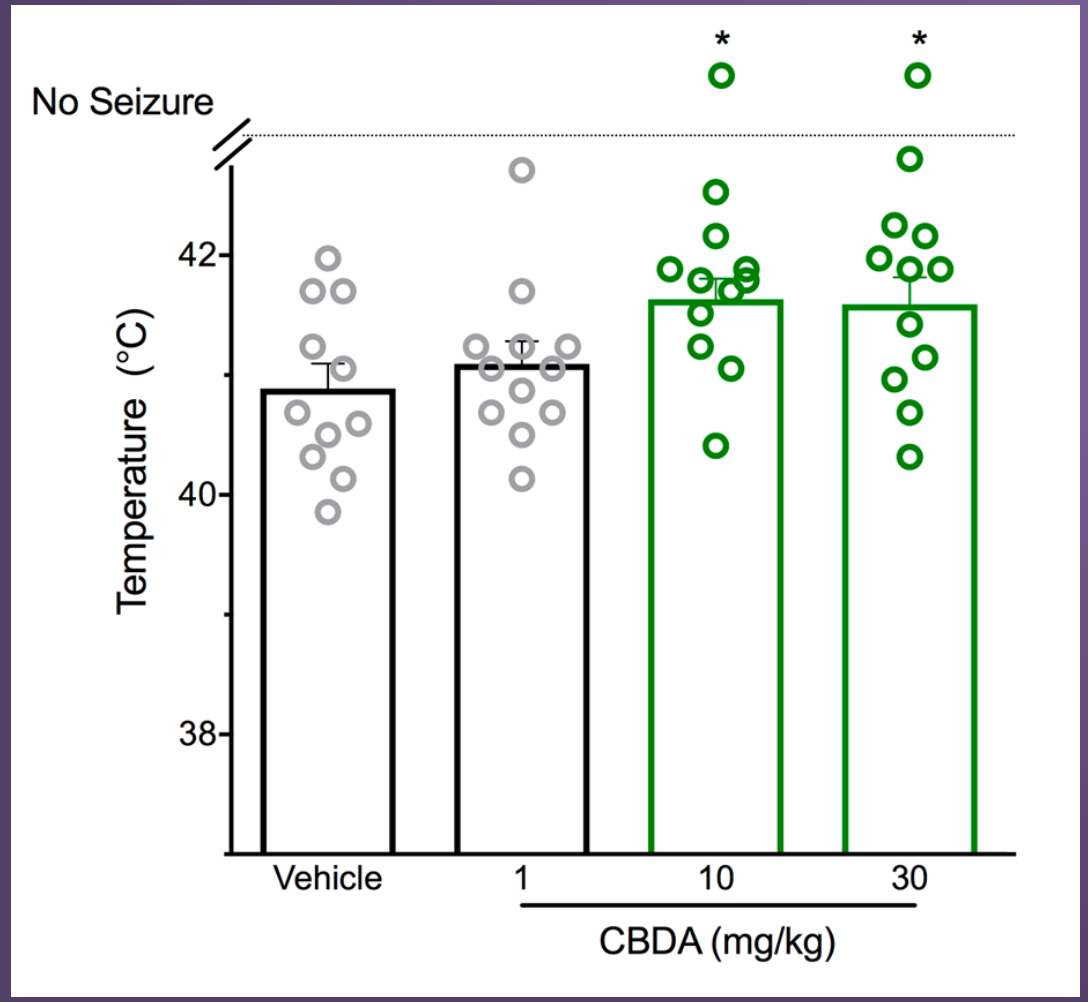

CBDA was anticonvulsant at 10 and 30 mg/kg, lower than the 100 mg/kg effective dose of CBD shown in two other studies

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Bonn-Miller, Marcel O., et al. "Labeling accuracy of cannabidiol extracts sold online." *Jama* 318.17 (2017): 1708-1709.

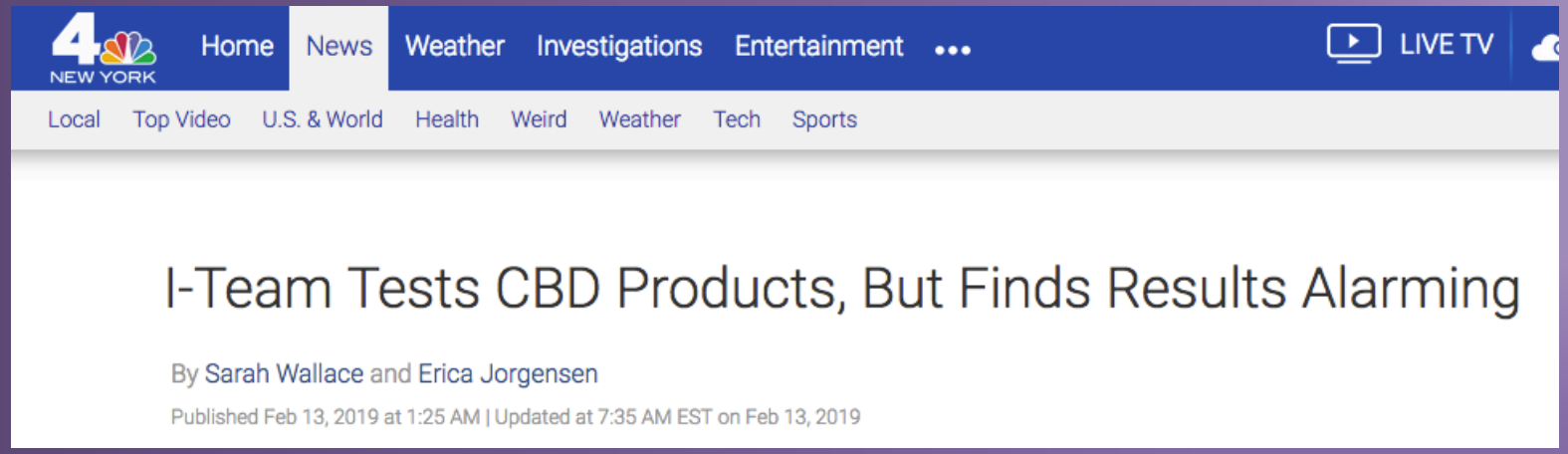
Table 1. Label Accuracy by Cannabidiol Extract Type

	Cannabidiol Extract Products	
	Oil (n = 40)	Tincture (n = 20)
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]
Median (range) [% of deviation]	2.76 (0.13-144.73) [12.11]	1.48 (0.01-22.30) [19.12]

[a] Cannabidiol content tested within 10% of labeled value.

[b] Cannabidiol content exceeded labeled value by more than 10%.

[c] Cannabidiol content tested more than 10% below labeled value.



- The I-Team's producer went online and undercover to local storefronts to purchase 3 brands of CBD oil and 4 brands of gummies (5 samples of each brand)
- One brand contained "four times the amount of lead than is approved. If a child gets their hands on these products, it could be life threatening,"
- One sample purchased from CBDistillery contained one pesticide that exceeds California's acceptable standards.
- Less than half of the samples that were tested actually had the stated amount of CBD inside the product

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- Sean Callan, PhD of Ellipse Analytics tested 240 CBD products for 300 contaminants labeling accuracy.
- 70% were found "highly contaminated" with heavy metals like lead and arsenic, herbicides like glyphosate, pesticides, BPA and toxic mold.
- One product had lead levels 100x EPA maximum for drinking water.
- More than half had labels that inaccurately reflected CBD concentration
  - Range from zero CBD to 6x the labeled potency

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Risk/Benefit Considerations

- Nearly one-third of patients with epilepsy have symptoms that are refractory to treatment (Kwan and Brodie, 2000).
- Although over 20 new seizure medications have been developed over the past several decades, the percentage of patients with medically intractable seizures has not changed significantly (French, 2007).

Risk/Benefit Considerations

- Failure of first antiepileptic drug (AED) strongly predicts failure to other AEDs and is associated with poor prognosis. (French, 2002)
- Children with absence epilepsy who fail first AED are 3x more likely to progress to myoclonic epilepsy and 8x more likely to intractable epilepsy. (Wirrel, et al., 2001)
- After failing 3 therapeutic regimens, chance of responding to 4^{th} is 12% in childhood epilepsy (Ramos-Lizana, et al. 2009)

Risk/Benefit Considerations

- Exacerbation of seizures during cannabis trial (uncommon)
- Cannabis withdrawal can potentiate seizures (Hedge et al., 2012)
  - Losing access to medicine
  - Inconsistent supply from one batch to the next
  - Hospitalization
  - Travel

CBD Interactions

- 39 adults and 42 children, Epidiolex 5-50mg/kg/d + AEDs
- Serum levels of topiramate, rufinamide, and N-des-methylclobazam increased in children and adults with increasing CBD dose
- Serum levels of zonisamide and eslicarbazepine increased in adults with increasing CBD dose
- Adult participants reported sedation more frequently with higher N-desmethylclobazam levels
- AST and ALT levels were higher in participants taking concomitant valproate with CBD

Gaston et al., 2017

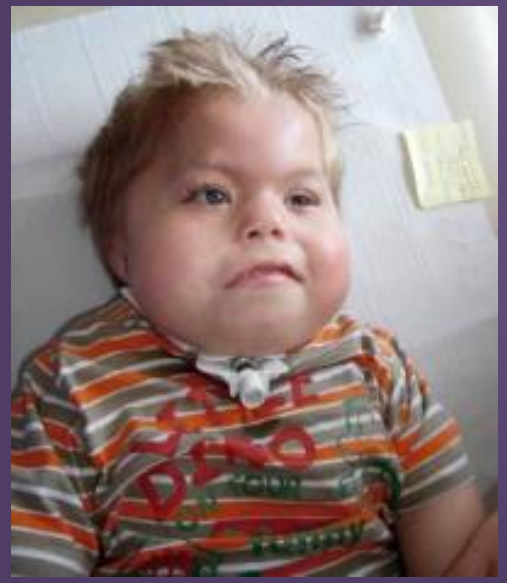
Rare Conditions and Palliative Care

Low Dose THC in Complex Pediatric Cases

- Use of dronabinol in 8 severely affected children with degenerative diseases, post-traumatic syndrome, epilepsy, hypoxic encephalopathy.
- Doses 0.04-0.12 mg/kg/d.
- Prominent positive changes noted in seizures, spasms, social interaction, with prominent palliation in fatal diseases.

Lorenz, R. 2004.

Gottschling, S. 2001. Cannabinoide bei Kindern Gute Erahrungen bei Schmerzen, Spastik und in der Onkologie. *Angewandte Schmerztherapei und Palliativmedizin*, 55-57.



- Dronabinol (average dose 0.2 mg/kg/d) was administered to 13 severely neurologically impaired children, aged 7 months -17 years with uniform benefit on spasticity and pain, improved sleep in 10.
- The longest treatment duration was five years, and no tolerance or dose escalation was apparent.
- 50 patients age 3 months+ were treated for nausea and inanition from chemotherapy. Marked benefit was noted with no serious side effects aside from one self-limited case of 10-fold accidental overdose, and no withdrawal effects were seen even after abrupt withdrawal after months of therapy.

Thank you!

Dustin Sulak, D.O.

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