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Cannabidiolo in Epilessia: quando, come e perché

- On behalf of the **CBD LICE study group**

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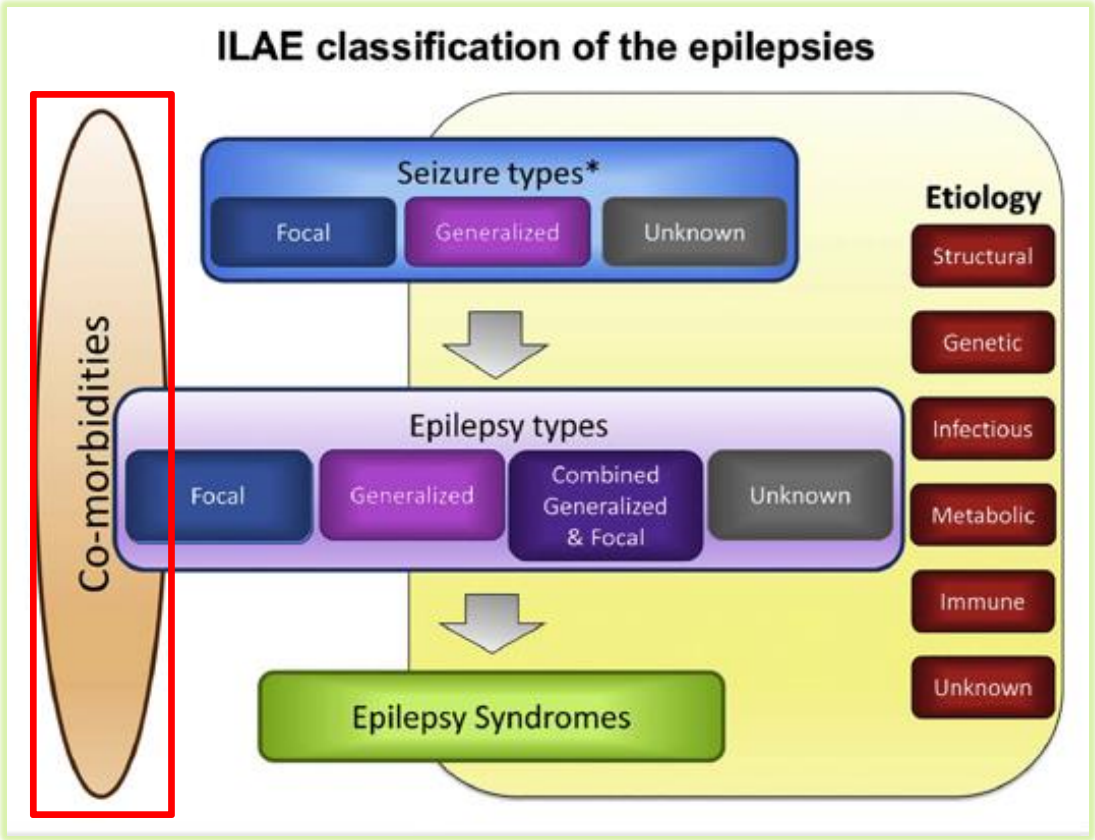
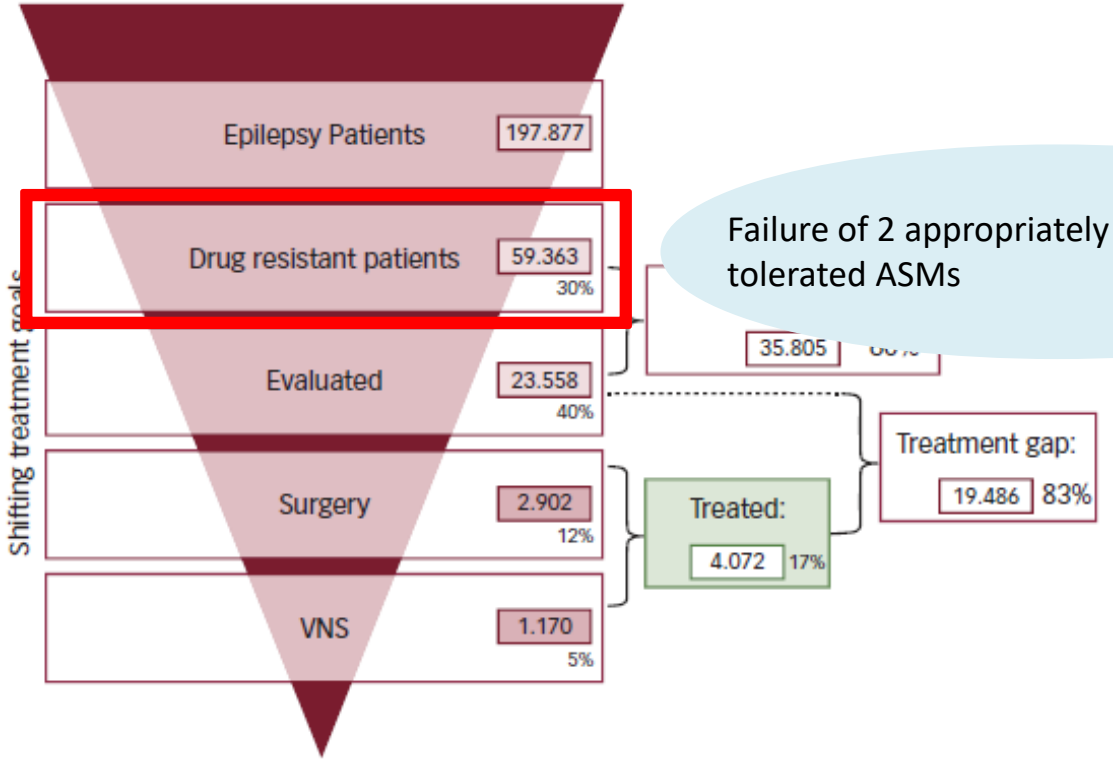


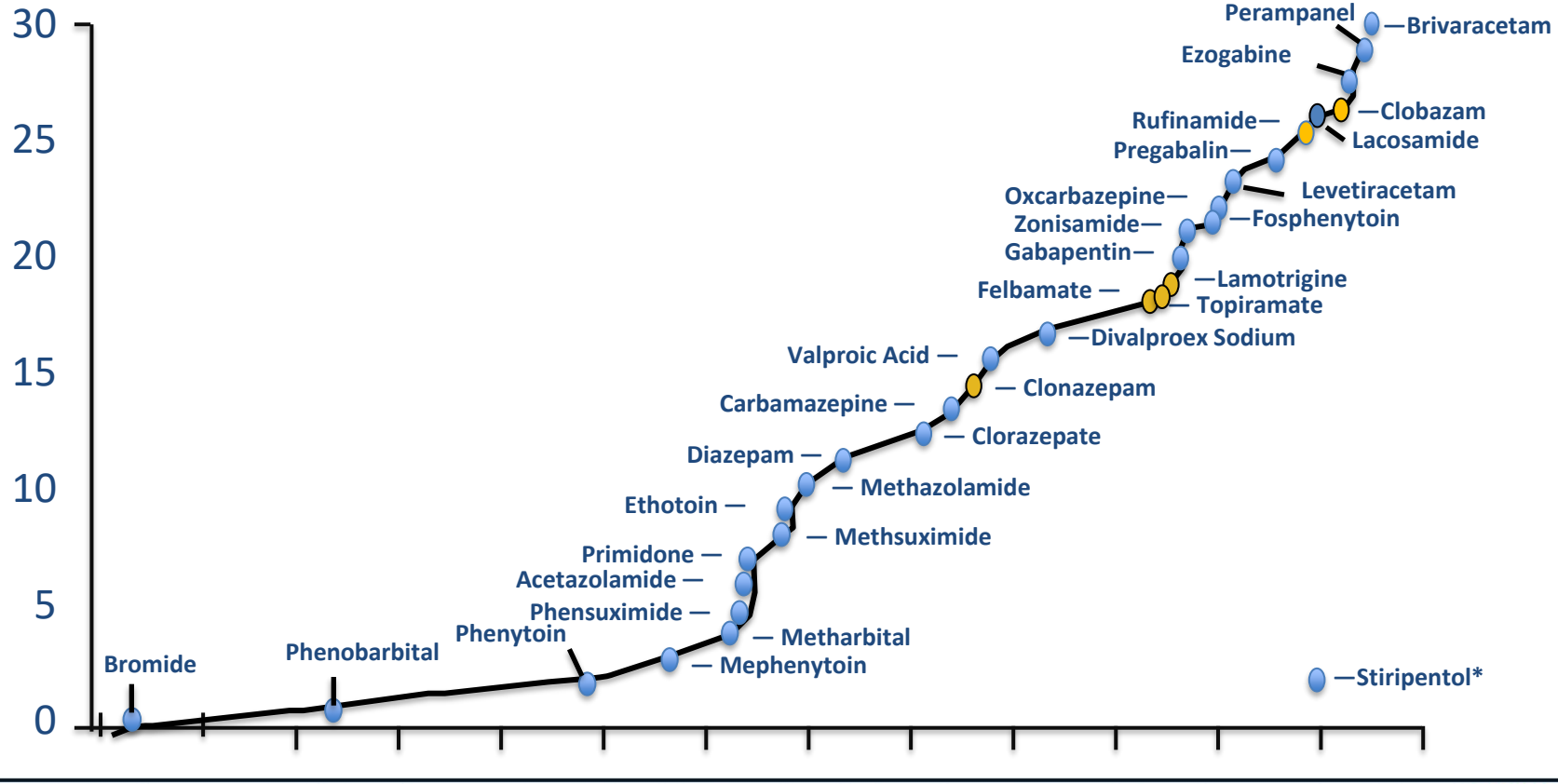
IE Scheffer et al. *Epilepsia.* 2017



Failure of 2 appropriately chosen and well-tolerated ASMs

VNS = vagus nerve stimulation.

Boon et al., 2015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Pregabalin
Rufinamide
Ezogabine
Perampanel
Mephenytoin
Metharbital
Methsuximide
Methazolamide
Clorazepate
Clonazepam
Divalproex Sodium
Topiramate
Lamotrigine
Fosphenytoin
Levetiracetam
Lacosamide
Clobazam
Brivaracetam
Stiripentol*
1860
1900
1920
1940
1960
1980
2000
2019

C. sativa L

- Little was actually known about cannabis therapy in Europe and America until O'Shaughnessy read a paper to a group of students and scholars of the Medical and Physical Society of Calcutta in 1839.[1]
- O'Shaughnessy conducted the first clinical trials of cannabis preparations, first with safety experiments on mice, dogs, rabbits and cats, then by giving extracts and tinctures (of his own devising, based on native recipes) to some of his patients.[1]
- O'Shaughnessy presented concise case studies of patients suffering from rheumatism, hydrophobia, cholera, and tetanus, **as well as a 40-day-old baby with convulsions, who responded well to cannabis therapy, leaping from near death to "the enjoyment of robust health" in a few days.[1]**

Historically Cannabis sativa L. was rich in both delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

1. http://antiquecannabisbook.com/chap1/Shaughnessy.htm; accessed 12 Oct 2018

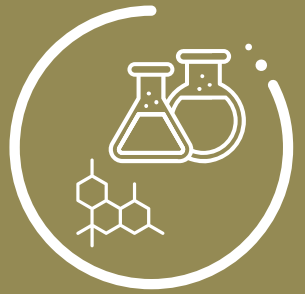
Phytocannabinoids

Aromatic hydrocarbons produced by the *Cannabis sativa* L plant

Endocannabinoids

Endogenous molecules in the body that bind and activate the cannabinoid CB_1 and CB_2 receptors

Synthetic cannabinoids



Synthetic molecules that are structurally similar to natural cannabinoids and/or interact with cannabinoid receptors

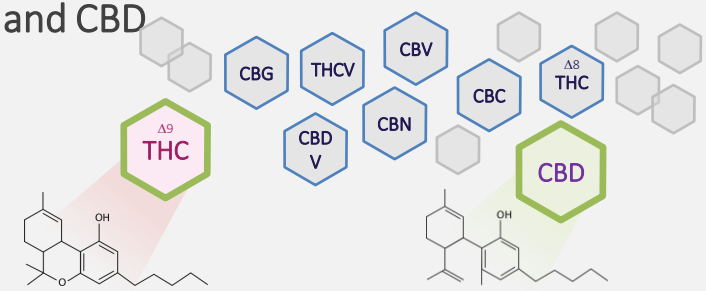
Terpenes and flavonoids

- Over 100 different terpenes in *C. sativa* strains
  - e.g. β-caryophyllene, a CB_2 antagonist
- Make up 3–5% of the dry mass of flowers
- Responsible for the distinctive scent and flavour profile in cannabis and many other plants (e.g. hops)
- Limited clinical evidence of direct medical properties

C. sativa L

Phytocannabinoids

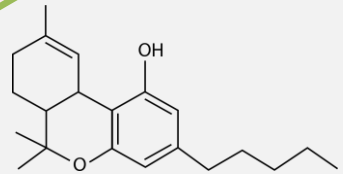
- Over 120 different phytocannabinoids
- Content and proportions vary with *C. sativa* strain (chemovar) and with environmental conditions
- The two characterised in most detail are THC and CBD



CBD and **THC** have different pharmacology, different effects, and different **potential medical applications**

THC

Δ^9Tetrahydrocannabinol

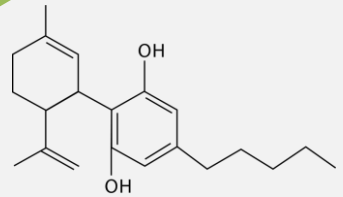


- Acts through **CB_1 receptors**, and other targets
- Is responsible for subjective intoxicating effects; used for both recreational and therapeutic purposes
- Many potential therapeutic actions

Include:
- Parkinson's Disease
- Pain
- Appetite
- Nausea and vomiting

CBD

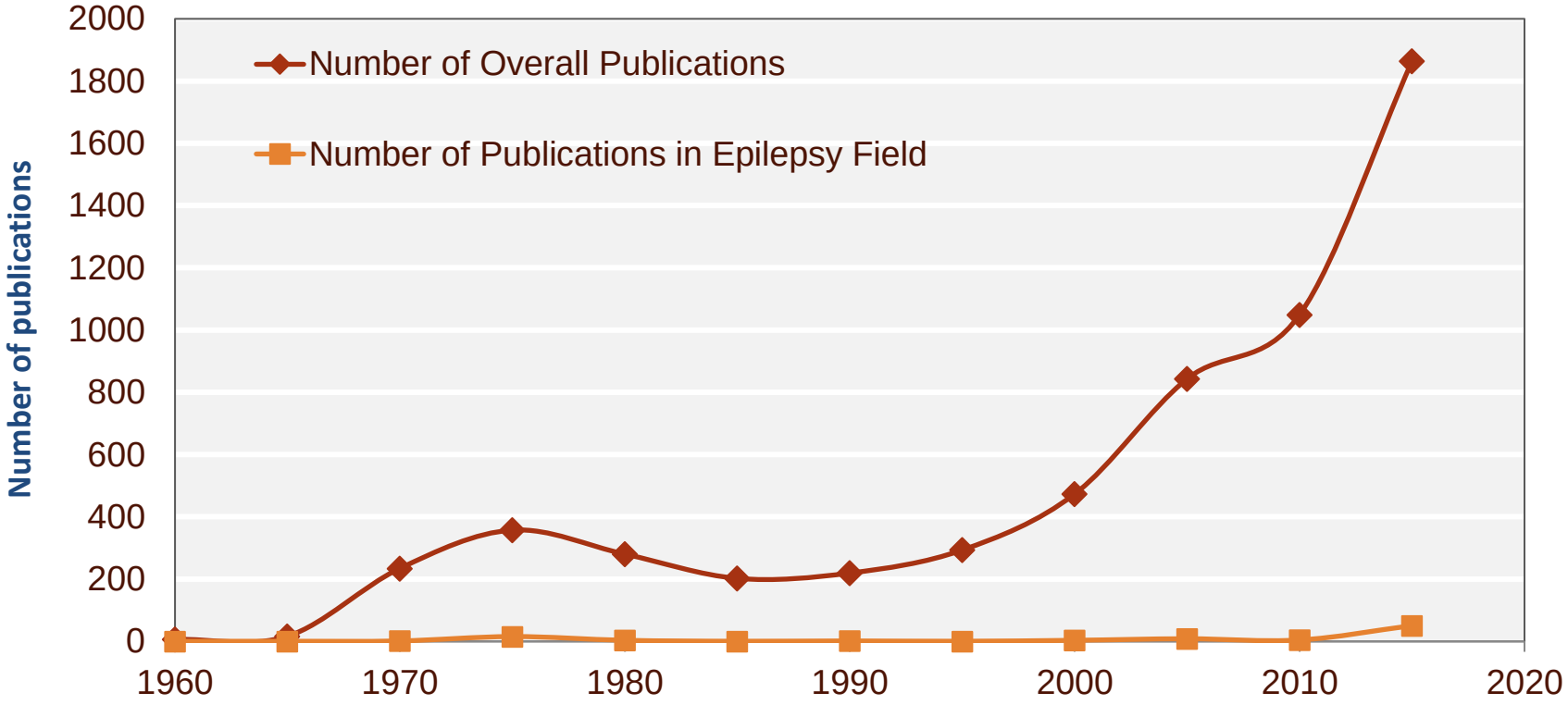
Cannabidiol



- Thought to act through multiple targets, predominantly **non-CB receptors**
- Not intoxicating
- Many potential therapeutic applications

Include:
- Epilepsy and seizures
- Addiction
- Psychosis
- Anxiety
- Neuroprotection

Cannabis-related publications overall and in epilepsy, by year



What CBD Is Not…

CBD is not structurally related to other ASMs[1]

CBD does not activate cannabinoid receptors at clinically relevant doses[2]

The anticonvulsant effect of CBD is not thought to be mediated through traditional sodium-dependent mechanisms[3,4]

CBD does NOT produce the euphoric effects like THC[1,2]

THC, tetrahydrocannabinol.

[1]Devinsky O et al. *Epilepsia*. 2014;55(6):791-802.
[2]Pertwee RG. *Br J Pharmacol*. 2006;147(1):S163-S171.
[3]Cilio MR et al. *Epilepsia*. 2014;55(6):787-790.
[4]Turner SE et al. *Prog Chem Org Nat Prod*. 2017;103:61-101.

CHARLOTTE's HEMP OIL (2013)

- A high concentration CBD/THC strain of cannabis produced by a medical marijuana group in Colorado

Parents began giving Charlotte low doses of plant extract and slowly increased the dose over time

Month 3: >90% reduction in generalized tonic-clonic seizures and weaned from other AEDs

Month 20: 2-3 nocturnal generalized tonic-clonic seizures per month, feeds and drinks by mouth by herself and autistic behaviors have improvement, walking and talking

Charlotte's Web, supplied by Realm of Caring, is based out of Colorado and parents and families are moving there to attempt treatment

http://www.cnn.com/2013/08/07/health/charlotte-child-medical-marijuana/

EPIDYOLEX® (cannabidiol) oral solution

GW Pharmaceuticals received, on 23 September 2019, European Commission approval for the marketing authorisation of EPIDYOLEX® (cannabidiol) oral solution

Epidyolex® is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older

Dravet Syndrome[1]

Lennox-Gastaut Syndrome[1]

GW Pharmaceuticals received, on 20 April 2021, European Commission approval for EPIDYOLEX® (cannabidiol) for the treatment of seizures associated with tuberous sclerosis complex

Epidyolex® is indicated for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older

Factor	LGS	DS
Treatment availability	• Limited options • Despite AED treatment, seizures persist in 80–90% of patients	• Limited options
Mortality	• The risk of death among children with LGS is reported as 14 times greater than that of the general population	• Mortality rate of 15.84 per 1,000 patient-years
Consequences of uncontrolled seizures	• Non-convulsive SE is common • Drop attacks occur in at least 50% of patients and can result in falls and injuries; tend to happen suddenly; protective headgear is required	• High risk of recurrent, prolonged convulsive seizures • Frequent SE in younger patients
Potential benefits of seizure control	• Improve cognition and behaviour • Reduce the risk of injury • Increase participation in school • Improve a patient's ability to self-care • Reduce impact on social and family relationships	• Greater degree of cognitive and behavioural improvement • Management of nocturnal seizures may: – improve QoL, developmental outcomes and seizure control – reduce the risk of SUDEP

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*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome

Orrin Devinsky, M.D., Anup D. Patel, M.D., J. Helen Cross, M.B., Ch.B., Ph.D., Vicente Villanueva, M.D., Ph.D., Elaine C. Wirrell, M.D., Michael Privitera, M.D., Sam M. Greenwood, Ph.D., Claire Roberts, Ph.D., Daniel Checketts, M.Sc., Kevan E. VanLandingham, M.D., Ph.D., and Sameer M. Zuberi, M.B., Ch.B., M.D., for the GWPCARE3 Study Group*

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome

Orrin Devinsky, MD, Anup D. Patel, MD, Elizabeth A. Thiele, MD, Matthew H. Wong, MD, Richard Appleton, MD, Cynthia L. Harden, MD, Sam Greenwood, PhD, Gilmour Morrison, and Kenneth Sommerville, MD, On behalf of the GWPCARE1 Part A Study Group

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Dr. Devinsky
Od4@nyu.edu

Neurology® 2018;90:e1204-e1211. doi:10.1212/WNL.0000000000005254

Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial

*Elizabeth A Thiele, Eric D Marsh, Jacqueline A French, Maria Mazurkiewicz-Beldzinska, Selim R Benbadis, Charuta Joshi, Paul D Lyons, Adam Taylor, Claire Roberts, Kenneth Sommerville, on behalf of the GWPCARE4 Study Group**

Lancet 2018; 391: 1085–96

- CBD has demonstrated ***efficacy*** and an acceptable ***safety*** profile in 4 phase III clinical trials and in expanded access programs (EAPs)
- To present the ***interim results*** on CBD safety and seizure outcomes from the Italian EAP

METHODS

Patient population and study design

- 30 Italian epilepsy centres enrolled LGS and DS patients from December 2018 through an open-label prospective EAP, with eligibility criteria according to placebo-controlled trials with up to the maximum of 20 mg/kg/day
- The protocol was approved by each site and written informed consent has been provided by patients or parents/caregivers. Overall data collection has been approved by the Ethics Committee, Catanzaro, Italy, protocol number 115/19

Procedures

- Data were collected on all seizure types, according to previous trials:
  - → Tonic, clonic, tonic-clonic, atonic, or secondary generalized convulsive seizures
  - → Non-convulsive seizures: myoclonic, absence, or myoclonic-absence seizures, and focal seizures

- During a 4-week baseline period, diaries of countable seizures have been provided by patients or parents/caregivers. Patients received an oral solution of purified CBD (100mg/mL; Epidyolex GW), starting dosage 5 mg/Kg/die up to 20 mg/Kg/die

- Visits/ assessment of adverse events have been performed after 2 weeks, 1, 3 and 6 months of treatment

Frontiers in Neurology Pub Date : 2021-03-31 , DOI:10.3389/fneur.2021.673135

Seizure frequency

→ provided per week since the first visit;

→ efficacy outcome assessed at 3, 6, 9 and 12 months

Weekly seizure frequency

→ converted to frequency per 28 days (weekly frequency × 4)

Seizure endpoints → **Response rate: percentage of patients with ≥50% and 100% reduction in monthly convulsive and total seizures compared to 4-week baseline**

Additional variables → status epilepticus, use of rescue medications, hospital admissions

- 93 patients were enrolled; median number of patients per site: 3 (range 1-11)
- In the safety dataset, twenty-nine (31.2%) dropped-out: reasons were lack of efficacy, AEs and one for concomitant use of other cannabis-derived products
- 82 patients with at least 3 months of treatment entered the effectiveness analysis

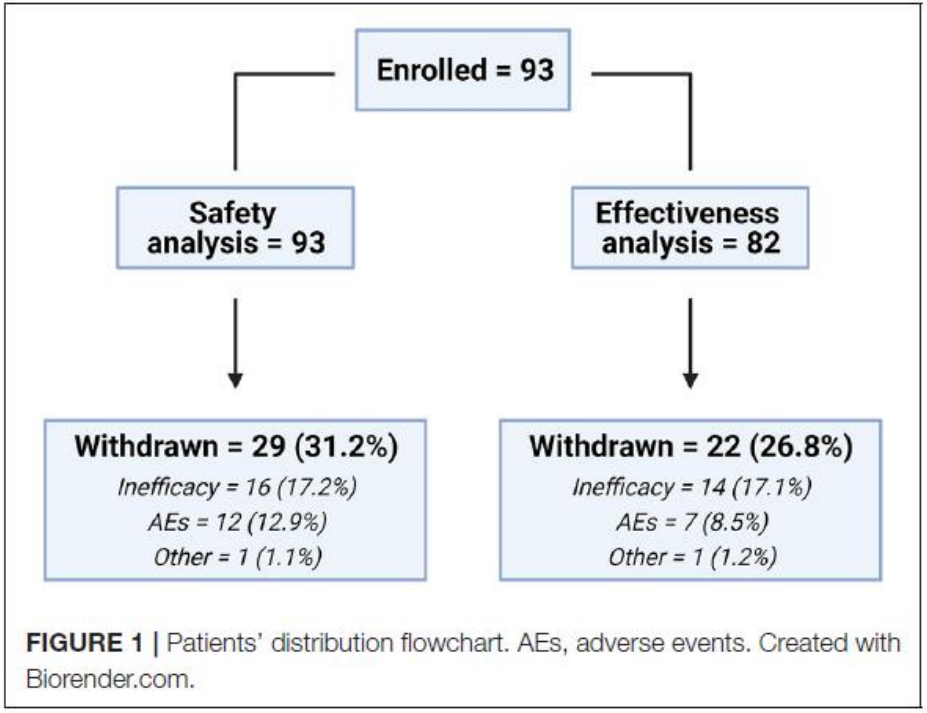

FIGURE 1 | Patients' distribution flowchart. AEs, adverse events. Created with Biorender.com.

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- Overall, the mean (SD) treatment duration was 8.7 (4.1) months, effectiveness data through 12 months was available for 51/82 patients (62.2%)
- In both analysis groups:

- mean age was 21 years (range 3-56 years)

-At baseline, the median monthly frequency of convulsive and total seizures was 49 and 71.5

TABLE 1 | Patients baseline demographic and clinical features.

	Safety (*n* = 93)	Effectiveness (*n* = 82)
Age (years), mean ± SD	21.4 ± 13.5	21.0 ± 13.1
Sex, male/female, *n* (%)	49 (52.7)/44 (47.3)	46 (56.1)/36 (43.9)
Body weight (kg), mean ± SD	50.8 ± 23.1	50.8 ± 21.9
Pediatrics/adults, *n* (%)	46 (49.5)/47 (50.5)	39 (47.6)/43 (52.4)
Diagnosis		
Dravet, *n* (%)	30 (32.3)	27 (32.9)
Lennox–Gastaut, *n* (%)	63 (67.7)	55 (67.1)
Concomitant ASMs taken at baseline, median (Q1–Q3)	3 (3–4)	3 (3–4)
Convulsive seizures/28 d, median (Q1–Q3)*	—	49 (12–147)
Total seizures/28 d, median (Q1–Q3)*	—	71.5 (23.6–181)

*ASMs, antiseizure medications. *During 4-week baseline period.*

Seizure Outcomes

TABLE 2 | Treatment response rate for convulsive seizures (A) and total seizures (B).

	Full cohort	Worsened	Unchanged	<50%	≥50%	Seizure-free
(A)						
Outcome 3 months, *n* (%)	82 (100)	11 (13.4)	21 (25.6)	24 (29.3)	24 (29.3)	2 (2.4)
Outcome 6 months, *n* (%)	71 (86.5)	8 (11.3)	13 (18.3)	17 (23.9)	29 (40.8)	4 (5.6)
Outcome 9 months, *n* (%)	61 (74.4)	7 (11.5)	9 (14.7)	14 (22.9)	28 (45.9)	3 (4.9)
Outcome 12 months, *n* (%)	51 (62.2)	6 (11.7)	6 (11.7)	12 (23.5)	23 (45.1)	4 (7.8)
(B)						
Outcome 3 months, *n* (%)	82 (100)	10 (12.2)	18 (22.0)	20 (24.4)	33 (40.2)	1 (1.2)
Outcome 6 months, *n* (%)	72 (87.8)	6 (8.3)	14 (19.4)	17 (23.6)	32 (44.5)	3 (4.2)
Outcome 9 months, *n* (%)	61 (74.4)	3 (4.9)	10 (16.4)	13 (21.3)	33 (54.1)	2 (3.3)
Outcome 12 months, *n* (%)	51 (62.2)	5 (9.8)	8 (15.7)	11 (21.6)	25 (49.0)	2 (3.9)

Total seizures included convulsive seizures (i.e., clonic, tonic, tonic–clonic, atonic, focal secondary generalized) and non-convulsive seizures (i.e., myoclonic, absence, myoclonic absence, focal with and without impaired consciousness). All response rate percentages are reported considering the total number of patients per follow-up. Seizure-free is not included in ≥50% cohort.

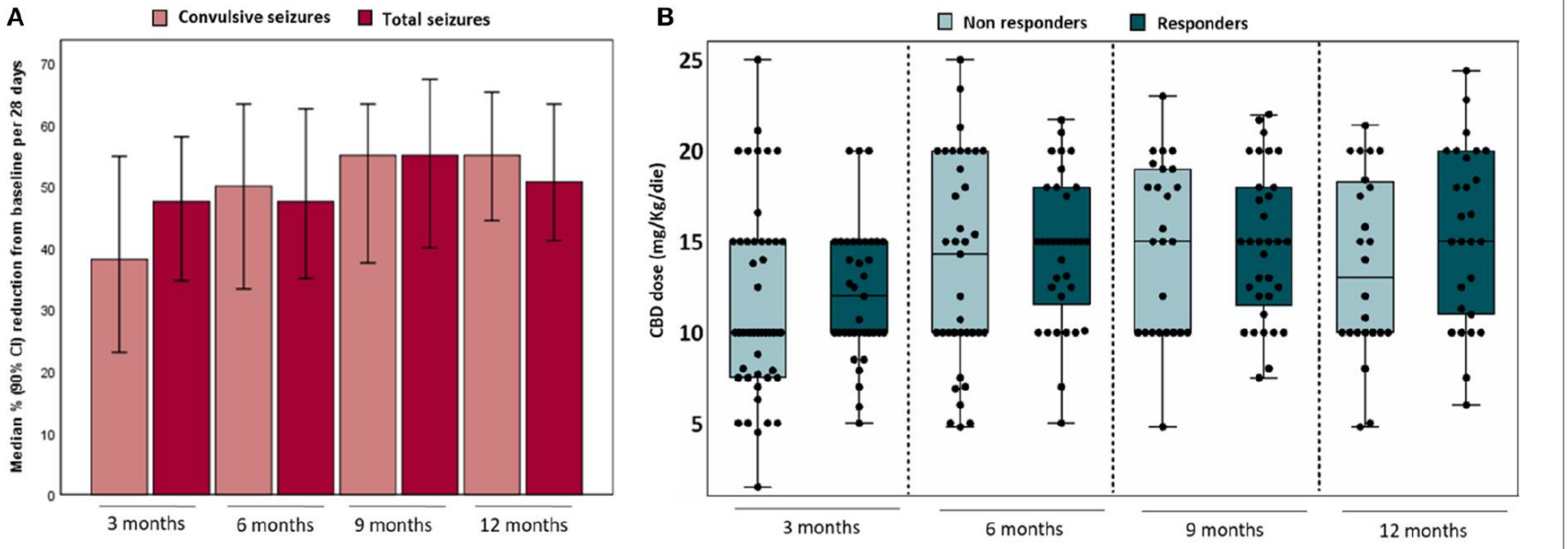

FIGURE 2 | Percentage reduction in median seizures per 28 days from baseline in convulsive and total# seizures for effectiveness analysis **(A)** and CBD doses related to achieving responder status at different outcomes **(B)**. #Total seizures included convulsive seizures (i.e., clonic, tonic, tonic–clonic, atonic, focal secondary generalized) and non-convulsive seizures (i.e., myoclonic, absence, myoclonic-absence, focal with and without impaired consciousness). NR, non-responders; R, responders (≥50% frequency reduction and seizure-free).

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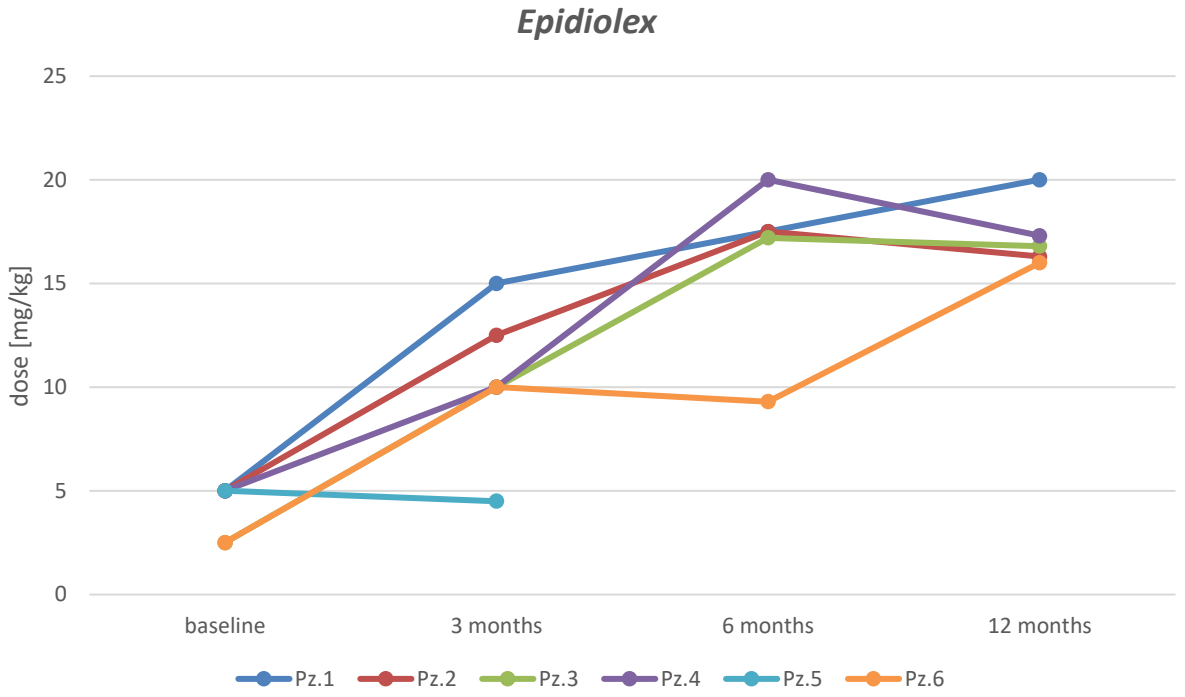
- 20 patients reduced the CBD dose at any time during follow-up
- Approximately 25% of the patients taking concomitant CLB and/or valproate modified their dose from baseline during the study

TABLE 3 | Dosing information coadministered ASMs.

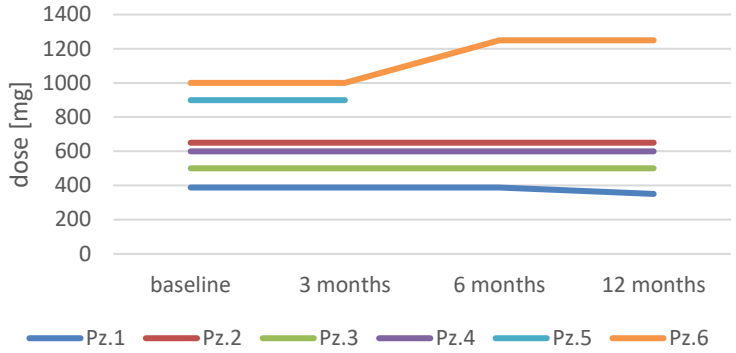
ASMs dose adjustment at all visits, *n* (%)	Valproate (*n* = 51)	Clobazam (*n* = 34)	Lamotrigine (*n* = 21)
Baseline dose stable	39 (74.5)	26 (76.5)	16 (76.2)
Baseline dose increased	1 (1.9)	0	0
Baseline dose decreased	8 (15.6)	1 (2.9)	3 (14.3)
Baseline dose increased and decreased	3 (5.9)	7 (20.6)	2 (9.5)

ASMs, antiseizure medications.

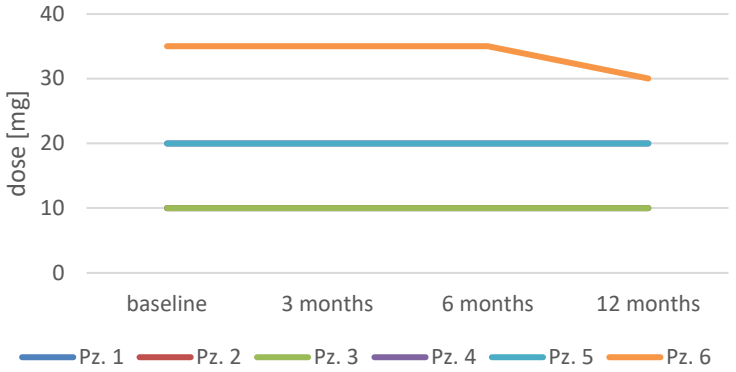
EPIDIOLEX AND OTHER ASMs DOSE ADJUSTMENTS DURING TREATMENT



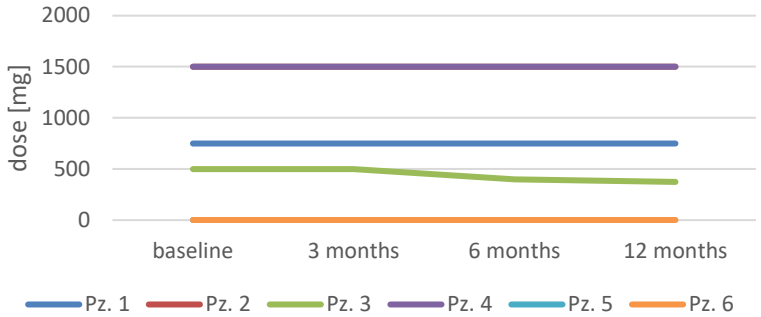
Valproic Acid



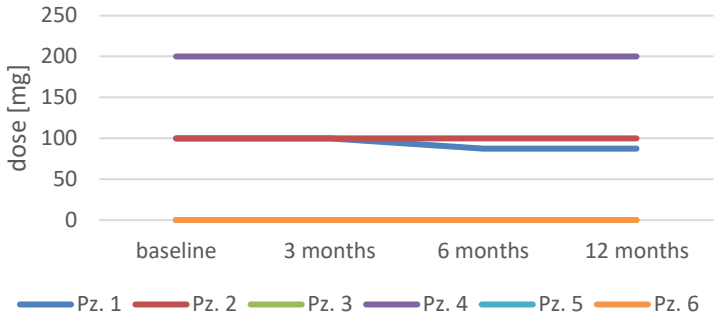
Clobazam



Stiripentol



Topiramate



Cannabidiol retention

- In patients with at least 1 month of treatment, the overall retention rate was 68.5% and log-rank tests were run to determine differences in the CBD retention rate for diagnosis (DS and LGS) or age (pediatrics and adults)
- The survival distribution was statistically significantly different for age, $\chi 2 = 7.38$, $p = 0.007$ (80.4% retention rate for patients ≥18 years), whereas no statistical significance was reached for diagnosis $\chi 2 = 3.04$, $p = 0.06$ (82.1% retention rate for Dravet syndrome)
- When considering the diagnosis in the age subgroups, DS pediatric patients have a higher retention rate than LGS patients ($\chi 2 = 9.96$, $p = 0.002$), while no difference was observed in adult patients

Epidyolex® is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older
Epidyolex® is indicated for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older

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Tolerability

In the safety analysis, 48 (51.6%) patients experienced at least one adverse event

The most common AEs reported were:

- ***somnolence*** (22.6%)

- ***diarrhea*** (11.8%)

- ***elevated liver enzymes*** (alanine aminotransferase/aspartate aminotransferase X3) (10.7%)

- ***loss of appetite*** (8.6%)

TABLE 6 | Summary of adverse events in safety analysis.

	CBD dose (mg/kg per day)			
	0–10 (*n* = 28)	11–15 (*n* = 29)	16–25 (*n* = 36)	All (*n* = 93)
Overall AE rate, *n* (%)	25 (89.3)	19 (65.5)	4 (11.1)	48 (51.6)
Overall serious AE rate, *n* (%)	3 (10.7)	4 (10.3)	1 (2.7)	8 (8.6)
AEs leading to CBD discontinuation, *n* (%)	4 (14.3)	6 (20.6)	2 (5.5)	12 (12.8)
AEs reported ≥2% in any group				
Somnolence, *n* (%)	12 (42.8)	7 (24.1)	2 (5.5)	21 (22.6)
Diarrhea, *n* (%)	3 (10.7)	3 (10.3)	5 (13.8)	11 (11.8)
Transaminases elevated, *n* (%)	4 (14.3)	3 (10.3)	3 (8.3)	10 (10.7)
Status epilepticus, *n* (%)	1 (3.5)	5 (17.2)	3 (8.3)	9 (9.6)
Loss of appetite, *n* (%)	6 (21.4)	1 (3.4)	1 (2.7)	8 (8.6)
Hyperammonemia, *n* (%)	5 (17.8)	1 (3.4)	1 (2.7)	7 (7.5)
Balance disorder, *n* (%)	3 (10.7)	2 (6.8)	1 (2.7)	6 (6.4)
Irritability, *n* (%)	0	3 (10.3)	1 (2.7)	4 (4.3)
Vomit, *n* (%)	2 (7.1)	0	1 (2.7)	3 (3.2)

In this cohort of highly treatment-resistant patients with Dravet syndrome and Lennox-Gastaut syndrome, ***add-on treatment of CBD for 12 months was associated with a reduction in seizure frequency and was generally well tolerated***

Overall, the percentage of patients achieving a seizure reduction ≥50% ranged from 40.2% to 54.1% for total seizures (in line with 38-52% in other studies and the 43-50% in an EAP)

A consistent percentage of patients achieved a seizure-free status compared to baseline after 3 months of treatment and during the 12 months follow-up period

The overall incidence of AEs was higher in the <10 mg/kg/die group than the other dose group, in contrast with the suggested dose effect (mainly for somnolence) reported in previous studies

One study reported thrombocytopenia in one-third of patients on cannabidiol and valproic acid. In our study, no cases occurred (62% of patients were on concomitant VPA)

Benefits of CBD Beyond Seizure Control?

QoLCE Subdomain	Baseline mean score (SD)*	Post-CBD mean (SD)*	*P* Value†
Energy/fatigue	42.26 (20.23)	52.28 (15.20)	.003
Memory	30.80 (16.19)	45.91 (12.96)	<.001
Control/ helplessness	49.00 (11.34)	56.07 (11.70)	<.001
Social interactions	25.01 (16.54)	37.60 (26.35)	.003
Overall QoL	**37.81 (7.78)**	**45.74 (8.50)**	**<.001**

*Higher scores reflect better quality of life.
†Unadjusted *P* values of mean difference between baseline and after treatment with CBD in an expanded access program.
Rosenberg EC, et al. *Epilepsia.* 2017;58:e96-e100.

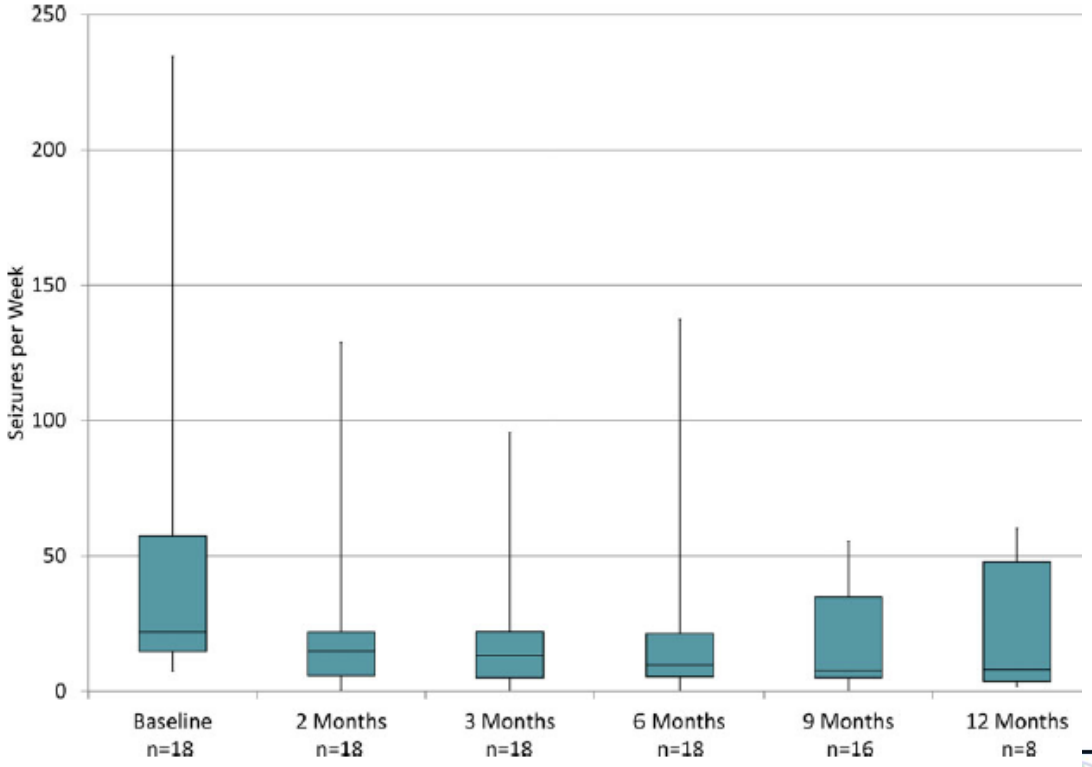
Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex

Evan J. Hess, Kirsten A. Moody, Alexandra L. Geffrey, Sarah F. Pollack, Lauren A. Skirvin, Patricia L. Bruno, Jan L. Paolini, and Elizabeth A. Thiele

Epilepsia, 57(10):1617–1624, 2016

Key Points

- Patients with refractory seizures in the setting of TSC had a median percent change in weekly seizure frequency of −48.8% after 3 months of treatment with CBD
- The responder rate after 3 months of treatment with CBD was 50%
- After 3 months of treatment with CBD, the median weekly seizure frequency decreased for all seizure types experienced by patients in this study
- Parents of patients reported cognitive gains in 85.7% of cases and behavioral improvements in 66.7% of cases with baseline cognitive or behavioral problems
- Most adverse events experienced in this study were temporary, of mild severity, and resolved through dose adjustments of CBD or concomitant antiepileptic drugs



The following may be mechanisms through which CBD provides some of its anticonvulsant effects

TRPV1

- CBD stimulates and desensitizes TRPV1 channels[1]

GPR55

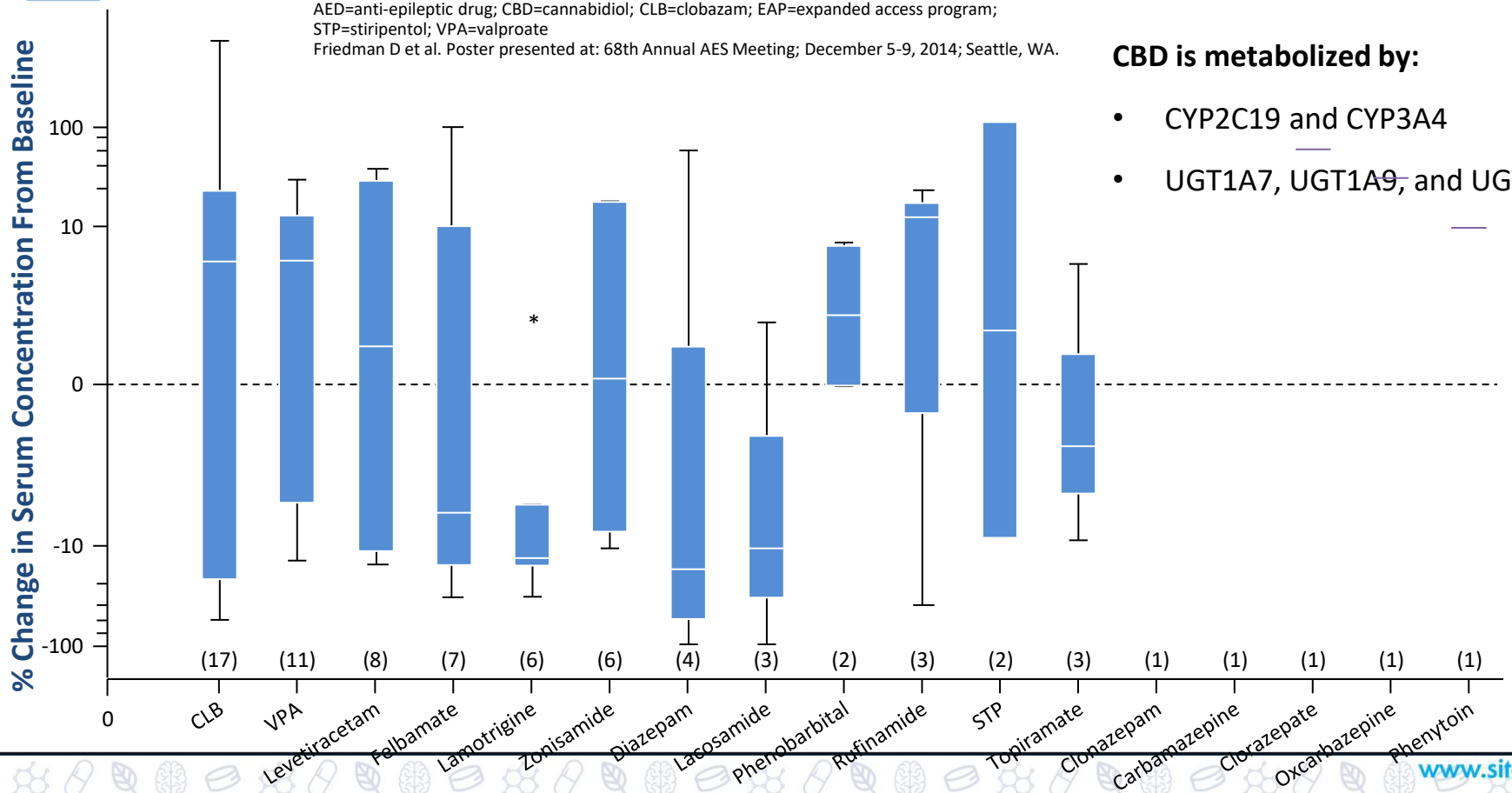
- CBD is an antagonist at the orphan receptor GPR55[2]

Adenosine

- CBD may modulate adenosine signaling[3]

The precise mechanisms by which CBD exerts its anti-convulsant effect in humans are unknown and are under investigation

CYP Enzyme	Effect of CBD BDS	
	Inhibitory	Induction
CYP3A4	✖	✖
CYP1A2	✖	✖
CYP2B6	✖	✖
CYP2C8	✖	
CYP2C9	✖	
CYP2C19	✖	
CYP2D6	✖	
CYP2E1	No effect	N/A



CBD is metabolized by:

- CYP2C19 and CYP3A4
- UGT1A7, UGT1A9, and UGT2B7

frontiers in Pharmacology

BRIEF RESEARCH REPORT
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A Volumetric Absorptive Microsampling Technique to Monitor Cannabidiol Levels in Epilepsy Patients

Sara Dubois[1†], Francesca Marchese[2†], Federica Pigliasco[3], Sebastiano Barco[3], Gino Tripodi[3], Tommaso Lomonaco[4], Simona Lattanzi[5], Emilio Russo[6], Giuliana Cangemi[3] and Pasquale Striano[1,2]*

TABLE 1 | Demographic and clinical features of the patients.

Patient/Age (years)	BMI (kg/m^2)	Total dose (mg/day)	Fraction (mg/day)	Concomitant antiseizure medications
#1/(4–6)	19.6	385 (17.5 mg/kg/day)	192 mg × 2 days	Valproic acid (378 mg/kg/day), stiripentol (750 mg/kg/day), clobazam (10 mg/kg/day), topiramate (100 mg/kg/day)
#2/(10–12)	28.1	650 (10 mg/kg/day)	325 mg × 2 days	Valproic acid (1,000 mg/kg/day), clobazam (15 mg/kg/day), levetiracetam (16 mg/kg/day)
#3/(16–18)	13.5	665 (17.5 mg/kg/day)	332 mg × 2 days	Valproic acid (650 mg/kg/day), stiripentol (1,500 mg/kg/day), topiramate (100 mg/kg/day)
#4/(25–27)	22.5	1,360 (20 mg/kg/day)	680 mg × 2 days	Valproic acid (600 mg/kg/day), stiripentol (1,500 mg/kg/day), clobazam (10 mg/kg/day), topiramate (200 mg/kg/day)
#5/(7–9)	14.7	230 (10 mg/kg/day)	115 mg × 2 days	Valproic acid (500 mg/kg/day), stiripentol (500 mg/kg/day)

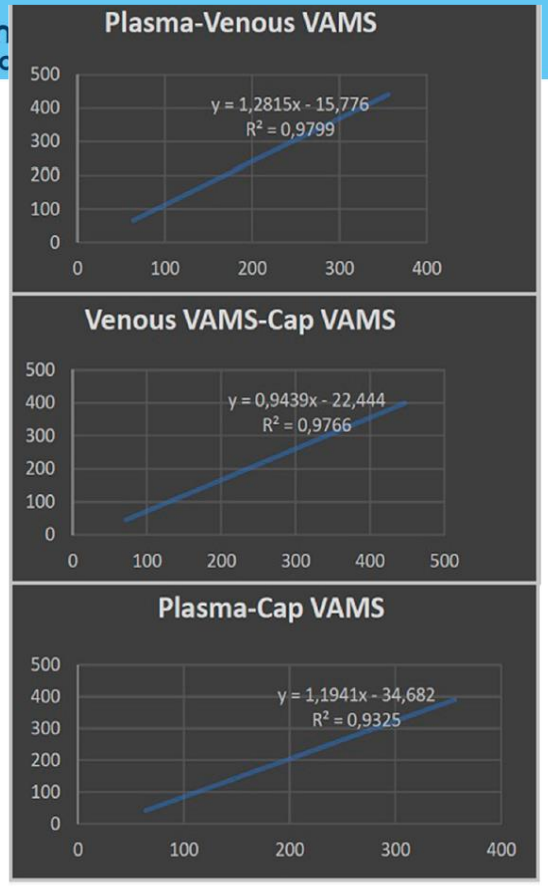

FIGURE 1 | Linear regression analysis showing the correlation between cannabidiol plasma levels from venipuncture and cannabidiol concentrations measured by venous and capillary volumetric absorptive microsampling (VAMS).

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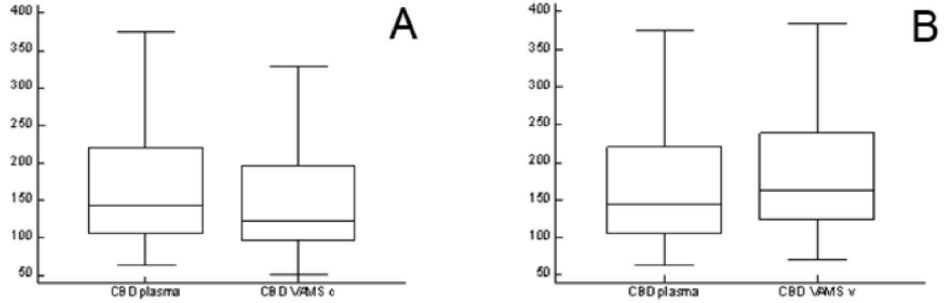
Cannabidiol Determination on Peripheral Capillary Blood Using a Microsampling Method and Ultra-High-Performance Liquid Chromatography Tandem Mass Spectrometry with On-Line Sample Preparation

Federica Pigliasco [1,†], Sebastiano Barco [1,†], Sara Dubois [2], Francesca March
Pasquale Striano [2,3,*], Tommaso Lomonaco [4], Francesca Mattioli [5], Gino
and Giuliana Cangemi [1]

Table 3. Characteristics of patients and results of CBD concentrations (expressed in µg/L) measured in plasma (p), venous (v) VAMS and capillary (c) VAMS.

	Dose (mg/kg/day)	Age (years)	Gender	CBD p (µg/L)	CBD VAMS v (µg/L)	CBD VAMS c (µg/L)
Patient 1	17.5	6	female	374	383.45	330.14
Patient 2	10.0	12	male	119	163.1	153.15
Patient 3	17.5	17	male	143	141.27	112.22
Patient 4	20.0	26	male	169	190.21	122.31
Patient 5	10.0	8	male	64	72.15	52.19

Results obtained from capillary blood were not statistically different from those obtained from venous blood (P = 0.69) or plasma (P = 0.69). Figure 2 shows the results of the Mann Whitney tests.



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Article

UHPLC-MS/MS Analysis of Cannabidiol and its Metabolites in Serum of Patients with Resistant Epilepsy Treated with CBD Formulations

Sara Malaca[1], Massimo Gottardi[2], Federica Pigliasco[3], Sebastiano Barco[3], Alessia Cafaro[3], Elisabetta Amadori[4,5], Antonella Riva[4,5], Martina Marcenaro[5], Pasquale Striano[4,5], Giuliana Cangemi[3,*], Roberta Pacifici[6], Simona Pichini[6] and Francesco Paolo Busardò[1]

Patient ID	Formulation	Dose of CBD (mg/kg/die)	Concentration (ng/mL)				
			6-α-OH-CBD	6-β-OH-CBD	7-OH-CBD	CBD-COOH	CBD
1	GW pharma CBD	15.25	1.15	0	27.11	380.32	239.74
2	GW pharma CBD	17.00	12.46	7.60	313.63	9707.01	279.75
3	GW pharma CBD	9.25	4.97	2.17	298.16	10112.23	130.12
		8.15	4.02	1.33	286.99	8849.05	105.74
4	GW pharma CBD	20.00	9.04	10.14	169.39	1510.89	343.81
			24.45	19.13	272.55	3200.88	396.31
5	GW pharma CBD	17.20	0	0.76	115.48	3030.12	80.29
			4.03	4.48	205.36	6616.54	170.63

The cannabinoid products that people are taking are very variable[1,2] – considerable inter and intra-variability

The stability of such products is variable[2-5]

The labelling accuracy varies enormously (e.g. only CBD on the label)[1,2,6]

- The CBD content varies enormously[1,2,6]
- Impurity content varies enormously (e.g. THC)[1]
- The non-cannabinoid fraction / vehicle can also vary enormously and affect product quality[1,3]

Products may contain unwanted items[10-13] such as:

- Bacterial or fungal contamination[13]
- Heavy metals[10,11,13]
- Pesticides[10,12,13]
- Organic solvents[13]

Companies which manufacture unregulated products have no obligation to maintain supply

ElSohly MA. Cannabis Phytochemistry and Overview of UM Research and Production Program. 2015 CBD Workshop.

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Article

Quality Traits of "Cannabidiol Oils": Cannabinoids Content, Terpene Fingerprint and Oxidation Stability of European Commercially Available Preparations

Radmila Pavlovic [1,2], Giorgio Nenna [3], Lorenzo Calvi [2], Sara Panseri
Luca Giupponi [1,2], Giuseppe Cannazza [6] and Annamaria Giorg

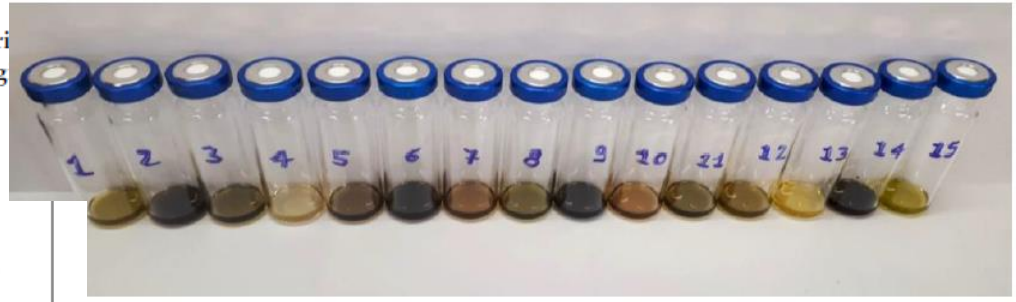


Figure 3. Different colors observed in CBD-based oil products.

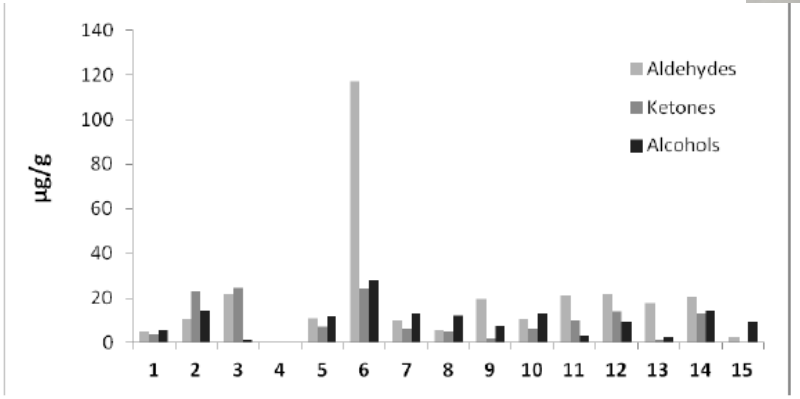
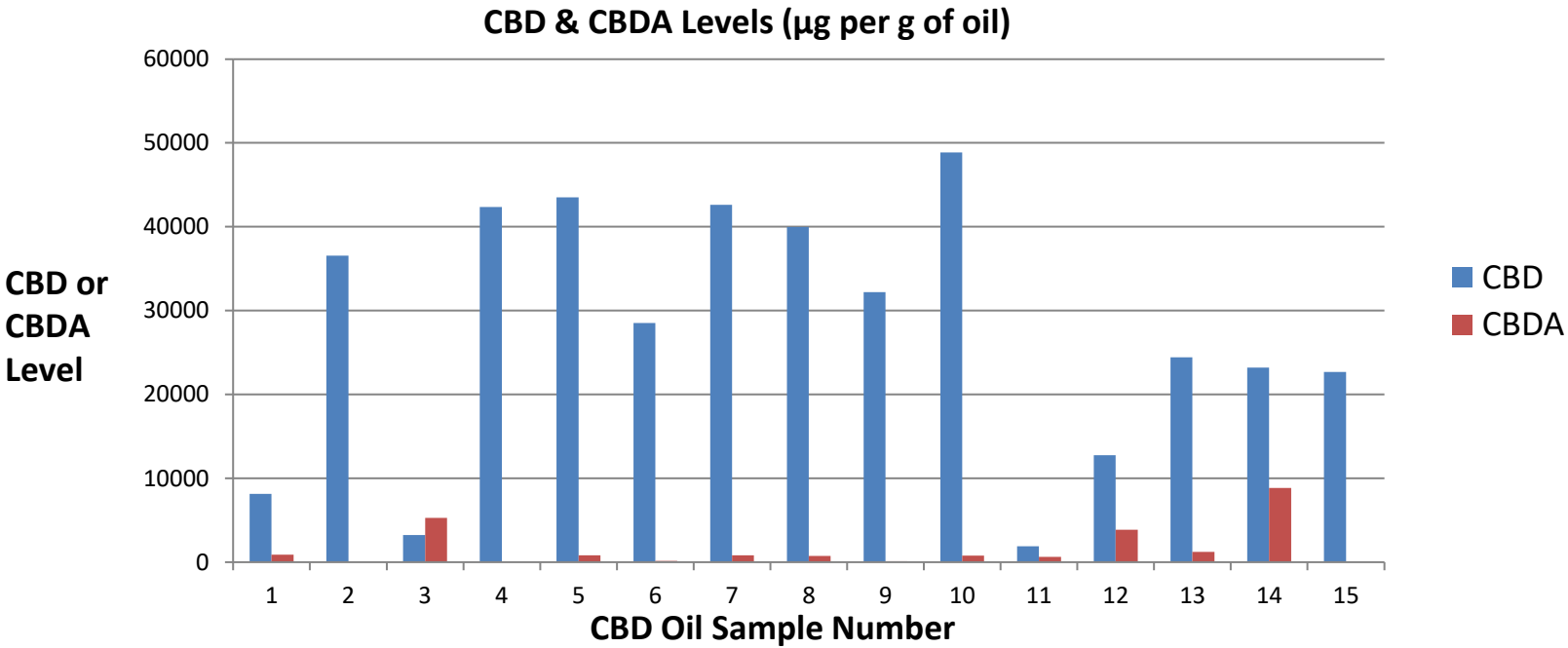


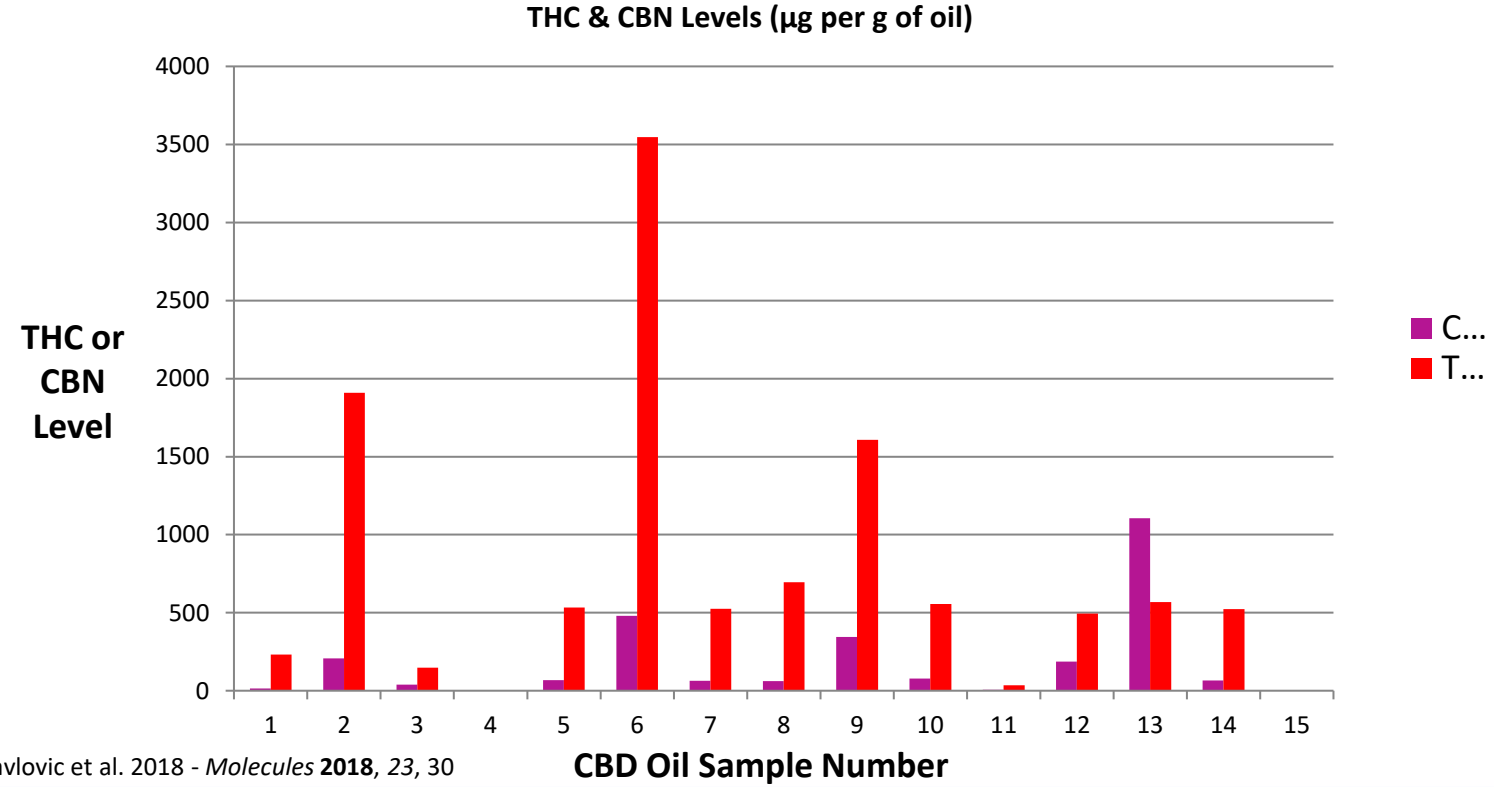
Figure 4. Lipid oxidation products quantified in CBD based oils preparations (expressed as µg/g SI equivalents).

Variability in CBD (and CBDA) content in 15 CBD oils bought online



Adapted from Pavlovic et al. 2018 - *Molecules* **2018**, *23*, 30

Total psychoactive cannabinoid (THC + CBN) content 15 CBD oils bought online



Adapted from Pavlovic et al. 2018 - *Molecules* **2018**, *23*, 30

Conclusions

- Historically CBD showed anticonvulsant activity in humans
- CBD is not like THC - it lacks the euphoric-like effects associated with THC
- GW CBD has demonstrated efficacy (vs placebo) in 3 RCTs in DS & LGS (MAA currently under review)
- Mechanism of CBD in epilepsy likely to be multi-modal – mechanism in humans is known - still under investigation
    - Bidirectional effect of CBD on Clobazam; No PK interaction with Valproate
- Cannabinoid products are available online with variable CBD & THC content, stability & unwanted impurities

Further Understanding of Mechanism and Predicting Treatment Response

Use in Other Types of Epilepsy/Neurological disorders (e.g., sleep disturbances, ASD)

Antiepileptic Potential of Other Cannabinoids (e.g., *cannabidivarin)*

CBD LICE study group

Luigi Francesco Iannone[1], Gabriele Arena[1], Domenica Battaglia[2], Francesca Bisulli[3,4], Paolo Bonanni[5], Antonella Boni[6,3], Maria Paola Canevini[7], Gaetano Cantalupo[8], Elisabetta Cesaroni[9], Manuela Contin[3,10], Antonietta Coppola[11], Duccio Maria Cordelli[12], Giovanni Cricchiuti[13], Valentina De Giorgis[14], Maria Fulvia De Leva[15], Marta De Rinaldis[16], Giuseppe d'Orsi[17], Maurizio Elia[18], Carlo Andrea Galimberti[19], Alessandra Morano[20], Tiziana Granata[21], Renzo Guerrini[22], Monica A. M. Lodi[23], Angela La Neve[24], Francesca Marchese[25,26], Silvia Masnada[27], Roberto Michelucci[28], Margherita Nosadini[29], Nicola Pilolli[24], Dario Pruna[30], Francesca Ragona[21], Anna Rosati[22], Margherita Santucci[6,3], Alberto Spalice[31], Nicola Pietrafusa[32], Pasquale Striano[25,26], Elena Tartara[19], Laura Tassi[33], Amanda Papa[34], Claudio Zucca[35], Emilio Russo[1], Oriano Mecarelli[36] and The CBD LICE Italy Study Group*

Conflict of Interest: FB has participated in clinical trials for GW Pharmaceuticals; received research grants, speaker fees or participated to advisory boards for Eisai, Cyberonics, UCB Pharma and Bial. MCa Canevini has participated advisory boards and/or received research fundings from UCB Pharma, Eisai, Italfarmaco, Cyberonics, Novartis, and the European Union. AC has received speaker fees by Eisai. CB has received speaker fees from Eisai, UCB Pharma, FB Health and Sandoz. Gd'O has served on the advisory board of Eisai. CG has received research grants and/or speaker fees from UCB Pharma, Eisai and Bial. TG received a speaker fee from GW Pharmaceuticals. RG has received consulting fees and speaker honoraria from Zogenix, Biomarin, UCB, Eisai, Novartis, GW Pharma, and Biocodex. OM has received consulting fees and speaker honoraria by Bial, Eisai, GW Pharmaceuticals and UCB Pharma. AL has received speaker's or consultancy fees from Eisai, Mylan, Sanofi, Bial, GW Pharmaceuticals and UCB Pharma. PP received speaker's fees from Eisai and UCB Pharma. AR received consulting fees from GW Pharmaceuticals. ER has received speaker fees and/or fundings and has participated in advisory boards for Eisai, Pfizer, GW Pharmaceuticals, UCB Pharma, Arvelle Therapeutics. NS has received grant support and fees for advisory board participation from GW Pharmaceuticals. PS developed within the framework of the DINOGMI Department of Excellence of MIUR 2018-2022 (legge 232 del 2016) and received speaker fees and participated at advisory boards for Biomarin, Zogenyx, GW Pharmaceuticals, Neuraxpharma; he also received research funding by ENECTA BV, GW Pharmaceuticals, Kolfarma srl., Eisai. ET has received speaker's fees from Eisai and Sandoz. AV received speaker's fees from Eisai, Italfarmaco, and GW Pharmaceuticals. MV received speaker's fees from Eisai and GW Pharmaceuticals.

Thank You for Your attention!

Istituto Giannina Gaslini

piano strategico