Cannabidiol in Epilepsy:

The indications, mechanisms and beyond

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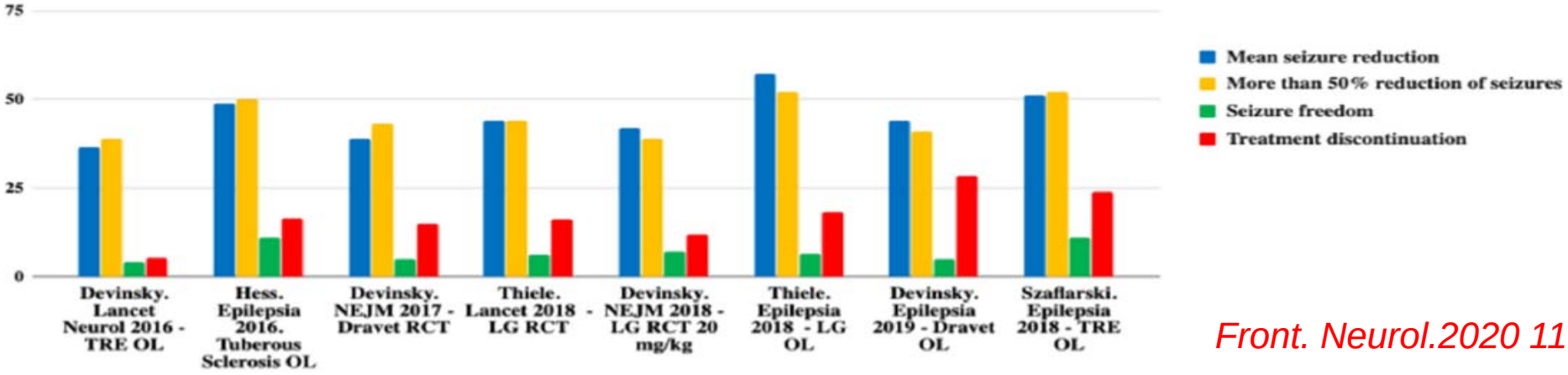
Major studies : CBD in epilepsy

TABLE 1 | Major studies about CBD in the treatment of epilepsy.

Study	Number of patients
Devinsky et al. (22) - TRE OL	214
Hess et al. (23) - Tuberous sclerosis OL	18
Devinsky et al. (24) - Dravet RCT	61
Thiele et al. (26) - LG RCT	86
Devinsky et al. (25) - LG RCT 20 mg/kg	76
Thiele et al. (30) - LG OL	366
Devinsky et al. (31) - Dravet OL	264
Szaflarski et al. (32) - TRE OL	607

TRE, treatment-resistant epilepsy; OL, open label; LG, Lennox-Gastaut; RCT, randomized controlled trial.

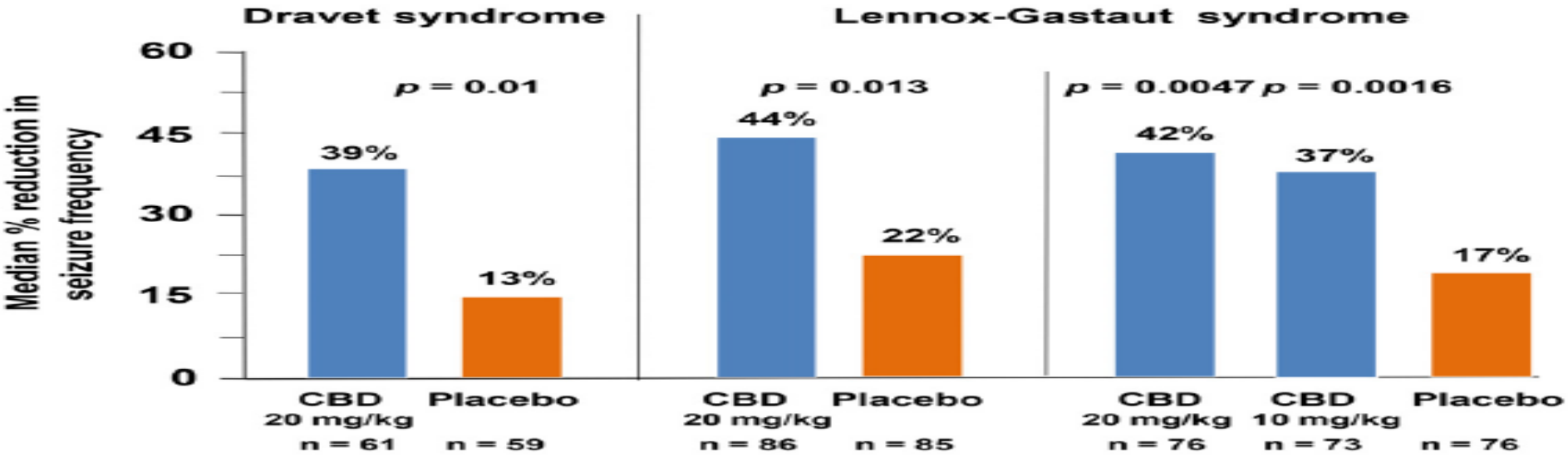


Front. Neurol.2020 11:531939

FIGURE 1 | Comparison of efficacy in the main studies. TRE, treatment-resistant epilepsy; OL, open label; LG, Lennox-Gastaut; RCT, randomized controlled trial. Adapted from (12).

Cannabidiol in Epilepsy , 3 RCT

Perruca E. Journal of Epilepsy Research Vol. 7, No. 2, 2017



↓Convulsive Sz

%Med Sz freq Reduction :
39%vs13% P=0.01

50% SR : 43%vs27% P=0.08

N Engl J Med.(2017) 376:2011–20.

↓Drop seizure

50%SR : 44% vs 24%
p= 0.0043

Lancet. (2018)391:1085–96.

50%SR : 20 vs 10 vs placebo
40% vs 36% vs 15%
p = 0.0006 p = 0.0030

N Engl J Med. (2018) 378:1888–97

Adverse Events : CBD purified

AEs Reported in the Open-Label Extension Study Data from Devinsky et al [1] and Thiele et al [2]

Dose CBD 20-30 mg/k/d

	DS n=264	LGS n=366
All-causality AEs, n (%)	246 (93.2)	337 (92.1)
AEs leading to withdrawal, n (%)	19 (7.2)	35 (9.6)
AEs reported in >10% of patients, n (%)		
Diarrhea	91 (34.5)	98 (26.8)
Pyrexia	72 (27.3)	69 (18.3)
Decreased appetite	67 (25.4)	65 (17.8)
Somnolence	65 (24.6)	86 (23.5)
Nasopharyngitis	41 (15.5)	
Convulsion	40 (15.2)	78 (21.3)
Vomiting	37 (14.0)	
Upper respiratory tract infection	36 (13.6)	53 (14.5)
Status epilepticus	29 (11.0)	
Fatigue	27 (10.2)	
SAEs, n (%)	77 (29.2)	94 (25.7)

	DS n=264	LGS n=366
SAEs reported in >1% patients, n (%)		
Status epilepticus	29 (11.0)	26 (7.1)
Convulsion	13 (4.9)	20 (5.5)
Pyrexia	10 (3.8)	
Pneumonia	7 (2.7)	9 (2.5)
AST increased	5 (1.9)	6 (1.6)
ALT increased		6 (1.6)
Hepatic enzyme increased		4 (1.1)
Pneumonia aspiration		6 (1.6)
Dehydration	4 (1.5)	
Influenza	4 (1.5)	
GTCSs	4 (1.5)	
Diarrhea	3 (1.1)	

Abbreviations: AE, adverse event; DS, Dravet syndrome; GTCSs, generalized tonic-clonic seizures; LGS, Lennox-Gastaut syndrome; SAE, serious adverse event.

1.Epilepsia. 2019;60(2):294–302

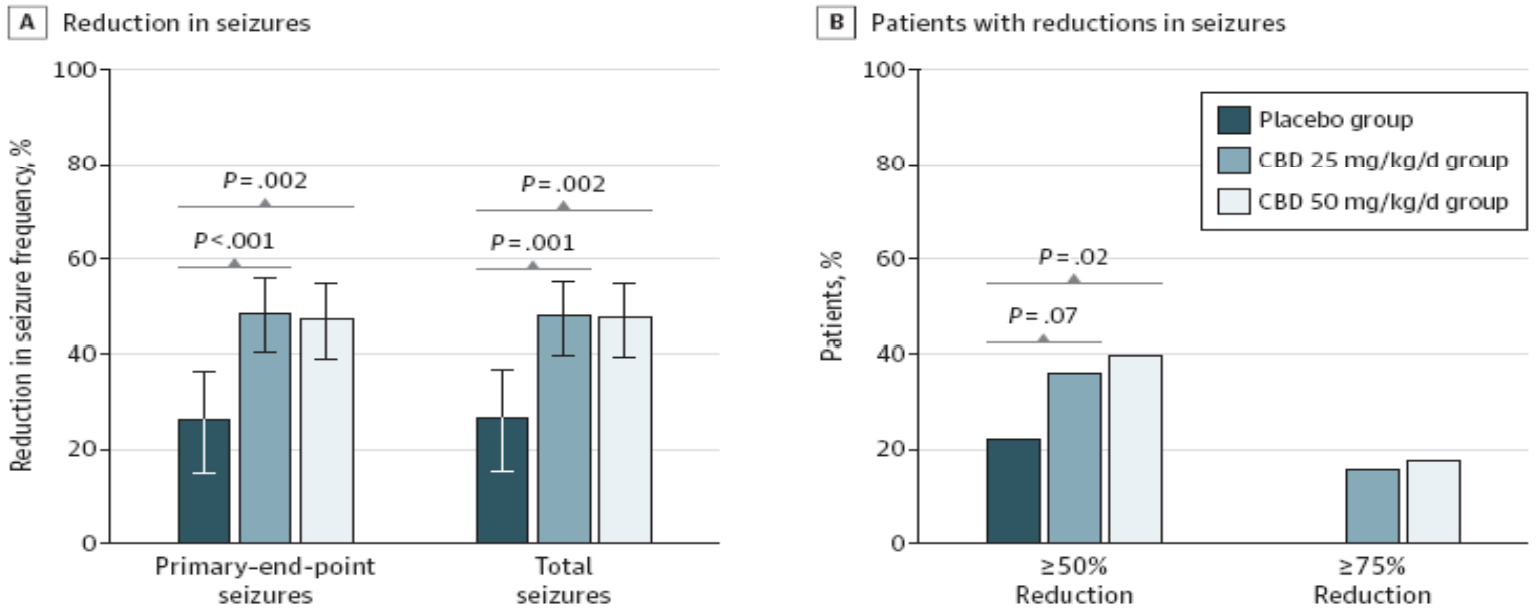
2. Epilepsia. 2019;60(3):419–428

Table from Neuropsychiatric Disease and Treatment 2020:16

Add-on Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex : RCT

TSC +DRE 224 cases : CBD 25 mkd : 50 mkd : placebo x 16 weeks

Figure 2. Seizure Outcomes During the Treatment Period



Cannabidiol significantly reduced TSC-associated seizures compared with placebo. The 25-mg/kg/day dosage had a better safety profile than the 50-mg/kg/day dosage.

JAMA Neurol. 2021;78(3):285-292.

Highly Purified Cannabidiol for Epilepsy Treatment: A Systematic Review of Epileptic Conditions Beyond Dravet Syndrome and Lennox–Gastaut Syndrome

Results 42 of 57 studies for the review. Included both pediatric and adult age.

- Across the trials, purified CBD was administered at dosages up to 50 mg/kg/day.
- RCT in TSC showed efficacy in greater seizure reduction than placebo in treatment period.
- Open-label studies suggested the effectiveness of CBD in the treatment of children and adults presenting with other epilepsy syndromes than those addressed by regulatory trials, including CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes, SYNGAP1 encephalopathy, and epilepsy with myoclonic absences.
- The most common adverse events observed during treatment with CBD included somnolence, decreased appetite, diarrhea, and increased serum aminotransferases.

Conclusions The currently available data suggest that response to treatment with a highly purified, plant-derived CBD oil based solution can be seen in patients across a broad range of epilepsy disorders and etiologies. The existing evidence can provide preliminary support for additional research.

CNS Drugs 2021, 35:265–281

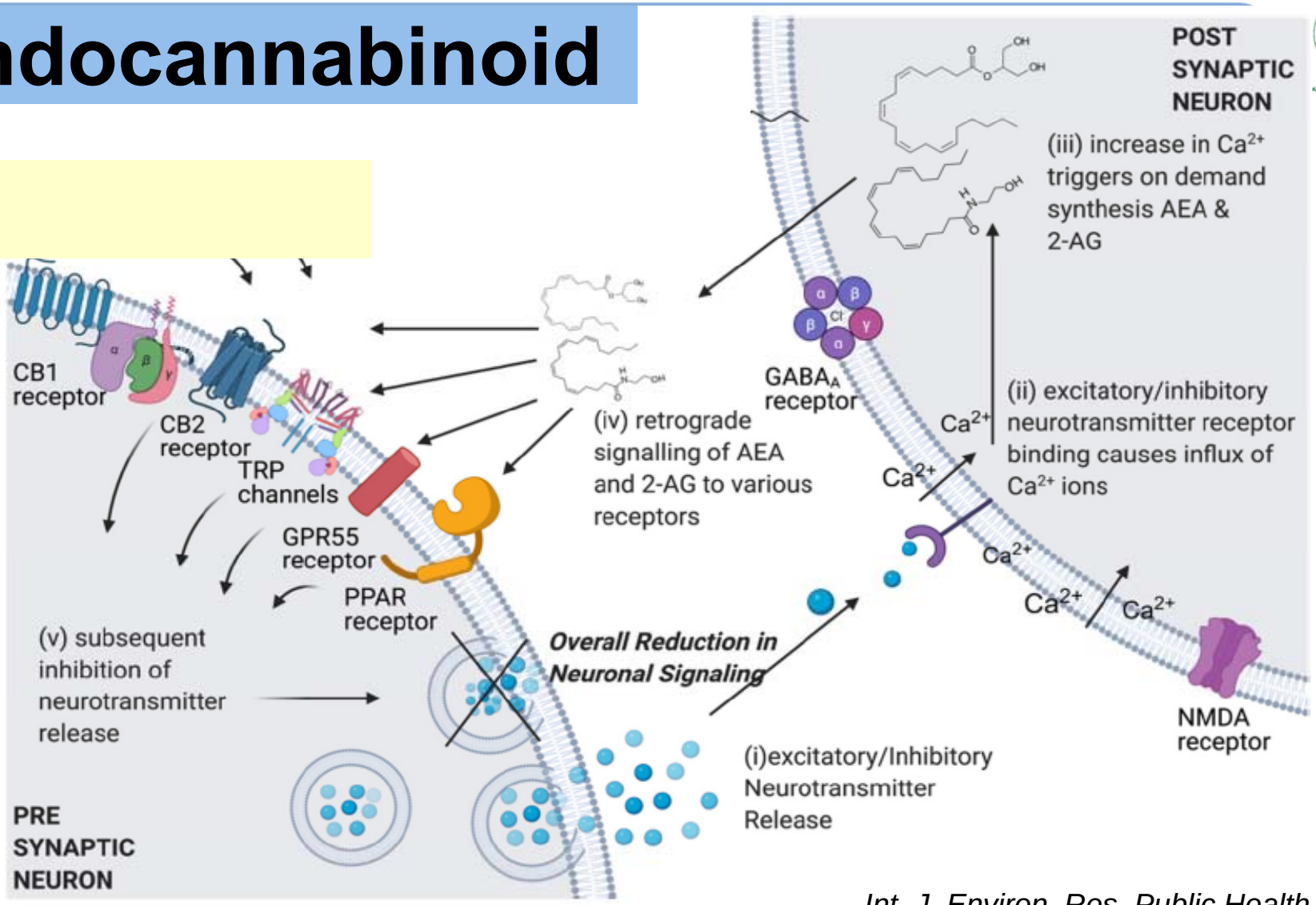
Why should cannabis be used in epilepsy?

- Unmet need and last resort for severe DRE
- New mechanism of action in antiseizure effect
- Improve other brain function/anti-epileptogenesis /neuroprotective effect ?

Endocannabinoid System (ECS)

- The ECS is a key modulatory system involving the cannabinoid receptor 1 (CB1) and 2 (CB2)
  - CB1 –presynaptic in olfactory bulb, C.cortex, striatum, hippocampus
  - CB2 – immune cell & hematopoietic cell, brain stem neuron
- The ECS plays an important role in the neuroprotection of acute neurological diseases, such as epilepsy, as well as chronic neurodegenerative diseases such as Parkinson's disease
- Endocannabinoids (AEA, 2AG) diffuse retrogradely to a presynaptic bouton and bind to receptors reducing the likelihood of release of the excitatory and inhibitory neurotransmitters

Endocannabinoid

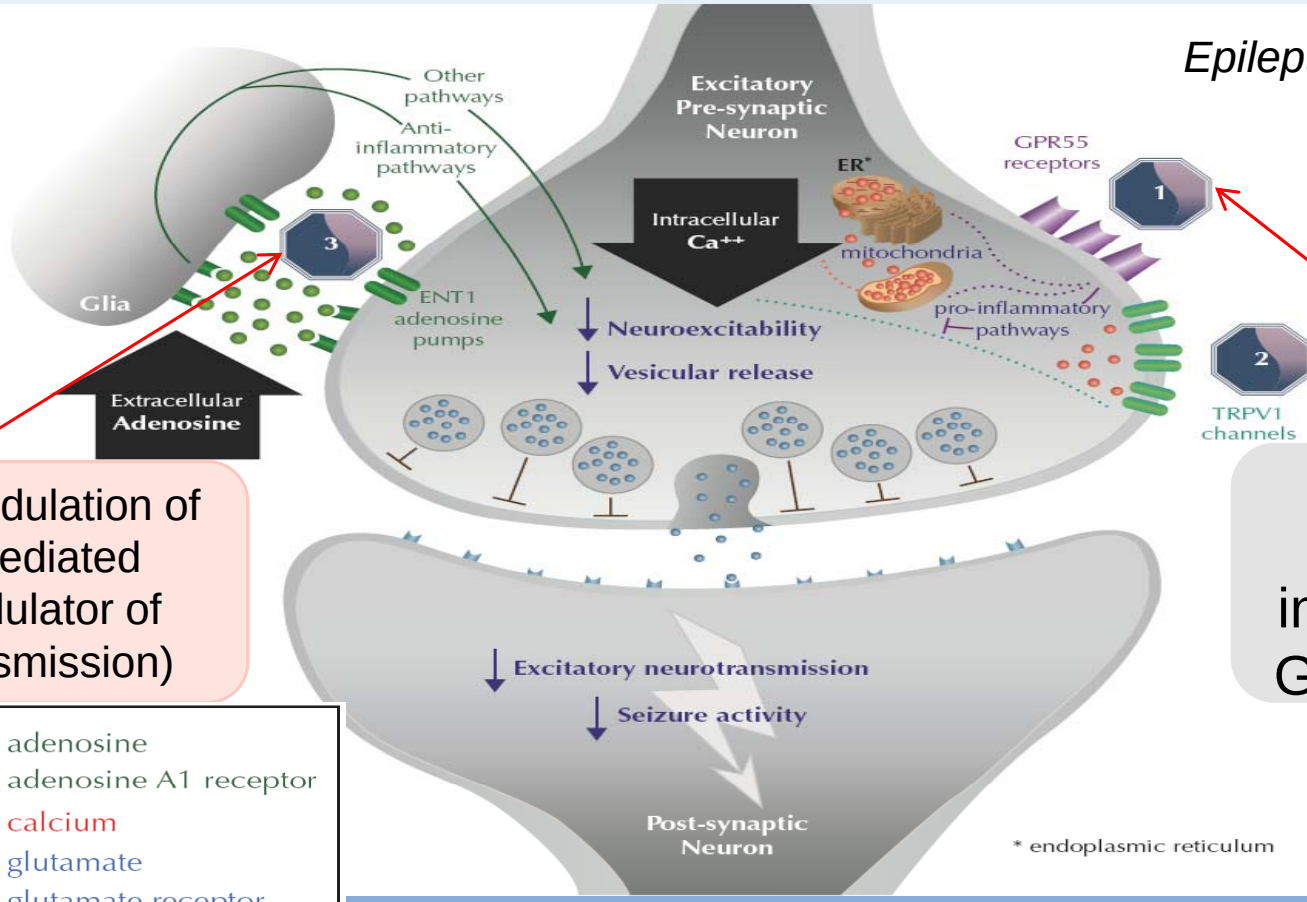


Int. J. Environ. Res. Public Health 2021, 18, 3993

Proposed mechanism of CBD in epilepsy.

CBD reduces neuronal excitability through functional antagonism of GPR55 receptors, desensitization of TRPV1 receptors and inhibition of adenosine transport

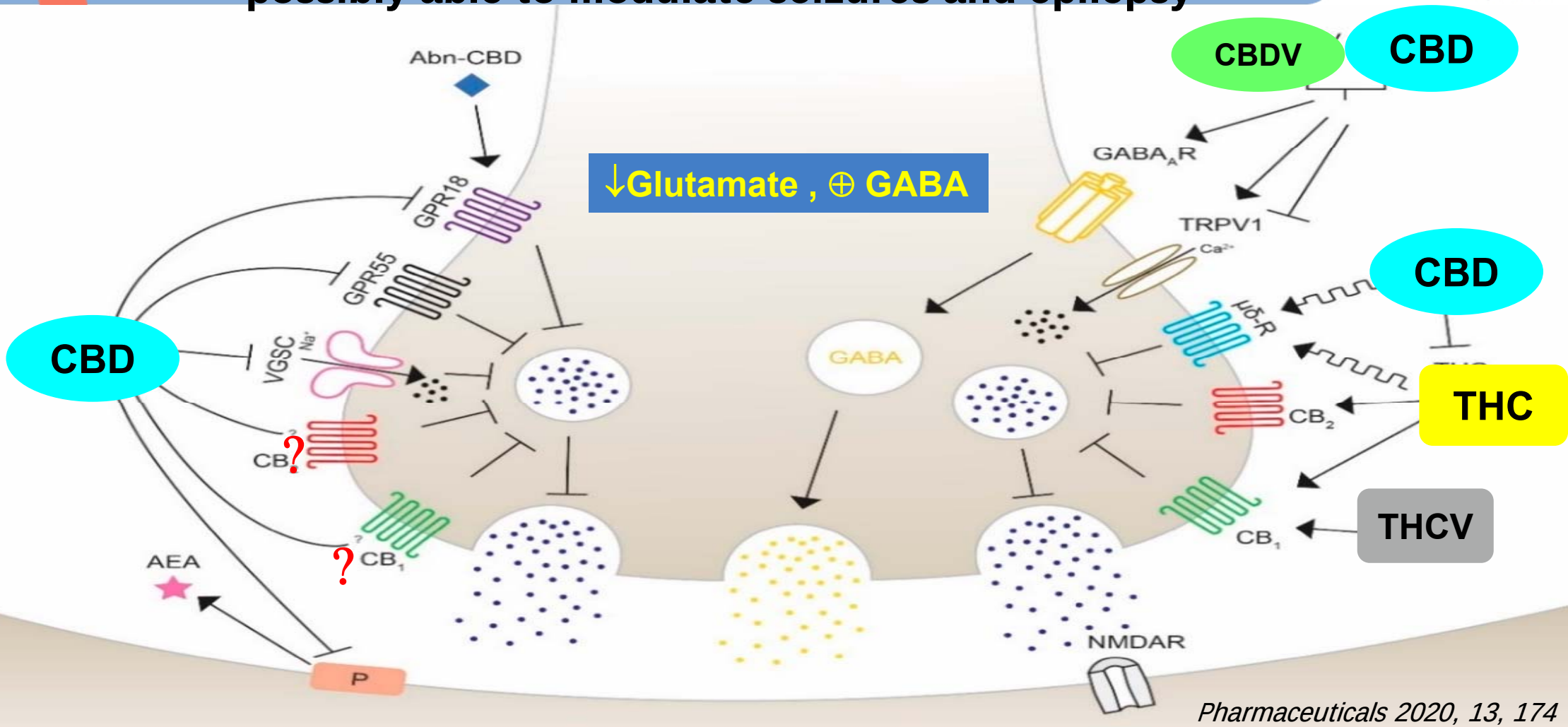
Epileptic Disord, 2020;22, Suppl1



CBD inh by-modulation of adenosine mediated (negative modulator of excitatory transmission)

CBD inh by modulation of intracellular Ca^{2+} (Via GPR55 & via TRPV1)

Overview of the action of different phytocannabinoids possibly able to modulate seizures and epilepsy



Pharmaceuticals 2020, 13, 174

Biosynthetic pathway of major phytocannabinoids

Pharmaceuticals 2020, 13, 174

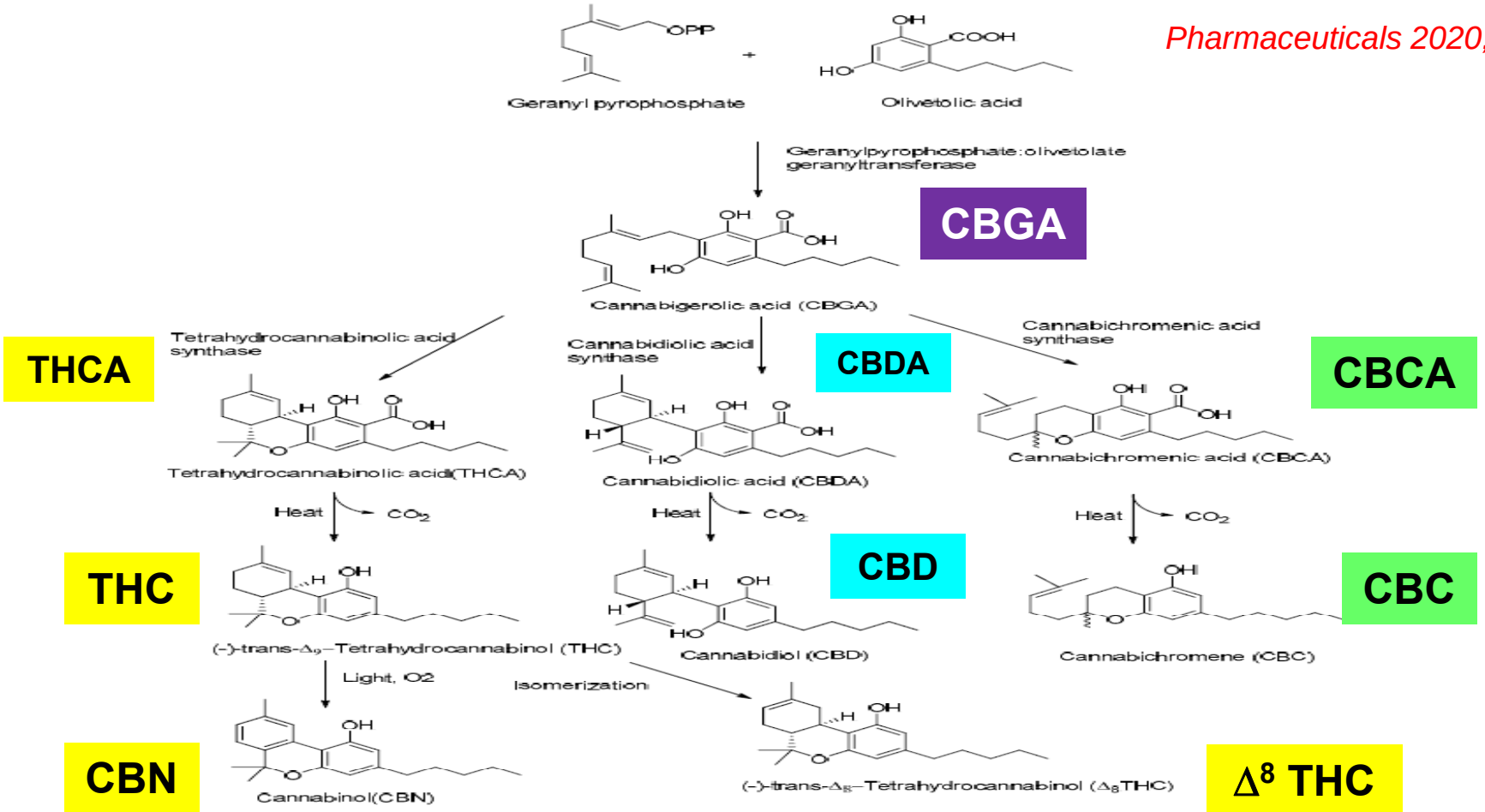
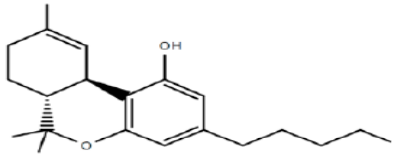
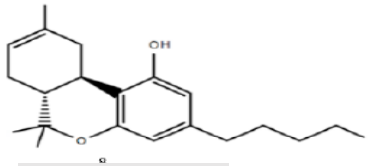


Figure 1. Biosynthetic pathway of major phytocannabinoids.

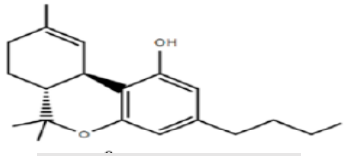
Phytocannabinoids : anticonvulsant activity



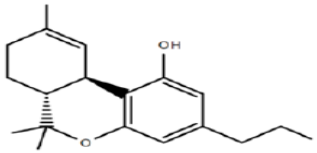
Δ^9 THC



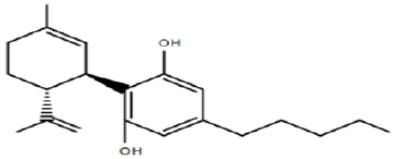
Δ^8 THC



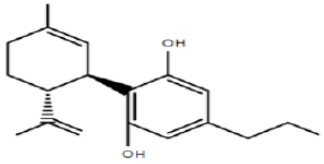
Δ^9 THCB



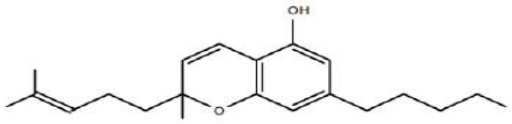
Δ^9 THCV



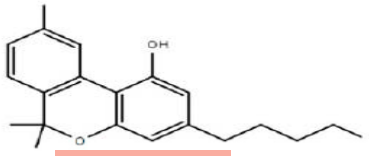
CBD



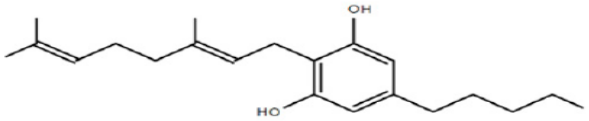
CBDV



CBC



CBN



CBG

Pharmaceuticals 2020, 13, 174

Figure 2. Structures of nine phytocannabinoids showing anticonvulsant activity; Δ^9-tetrahydrocannabinol (Δ^9-THC), Δ^8-tetrahydrocannabinol (Δ^8-THC), Δ^9-tetrahydrocannabutol (Δ^9-THCB), Δ^9-tetrahydrocannabivarin (THCV), cannabidiol (CBD), cannabidivarin (CBDV), cannabichromene (CBC), cannabinol (CBN), cannabigerol (CBG).

CBDV, Δ9-THCV and CBG have

- Anticonvulsant characteristics combined with favorable side-effect profiles
- Clear neuroprotective/neurogenerative characteristic has been identified

Int. J. Environ. Res. Public Health 2021, 18, 3993

Cannabidivarin (CBDV)

Direct CBD analogue derived from cannabigerovarin

- CBDV inhibits the reuptake of AEA and 2-AG at micro- and nano-molar concentrations , respectively
- CBDV has been shown to dose dependently activate these channels (TRPV1, TRPV2 and TRPA1) makes it a novel target for treating epilepsy symptoms.
- In a randomised block design participants received 400-mg CBDV over a treatment period of 14 days. It was observed that CBDV did not significantly reduce seizure instances.
- Suspected inefficacy of purified CBDV vs CBDV-rich ??

Neuropsychiatr. Dis. Treat. 2020, 16, 381–396

Delta-9-Tetrahydrocannabivarin (Δ^9-THCV)

- CBDV isomerises into Δ^9-THCV → potential Rx epilepsy
- Δ^9-THCV exhibits antagonist actions at both CB1 and CB2 receptors : inhibiting seizure like activity through a non-CB1 receptor-mediated mechanism
- Little evidence is currently available to conclude that Δ^9-THCV is not effective in treating the symptoms of epilepsy

J. Cannabis Res. 2020, 2, 1–6.

Cannabigerol (CBG)

Major phytocannabinoids present in Cannabis sativa

- Agonist for both CB1 and CB2 receptors
- Agonist of TRPA1, TRPV1, TRPV2 channels, antagonist of TRPM8 channels.
- Endocannabinoid reuptake inhibitor
- Antagonist of serotonin receptors, 5-HT2A receptor signalling → control of neuronal excitability through GABAergic, monoaminergic & glutamatergic neurotransmission
- CBG activates α2-adrenoreceptors and blocks activity at 5-HT1A receptors → anticonvulsant potential
- Lack of pre-clinical research specifically analysing CBG's efficacy as an anticonvulsant
- Begin investigating CBG- potential enhancer of other compounds, 'entourage effect'

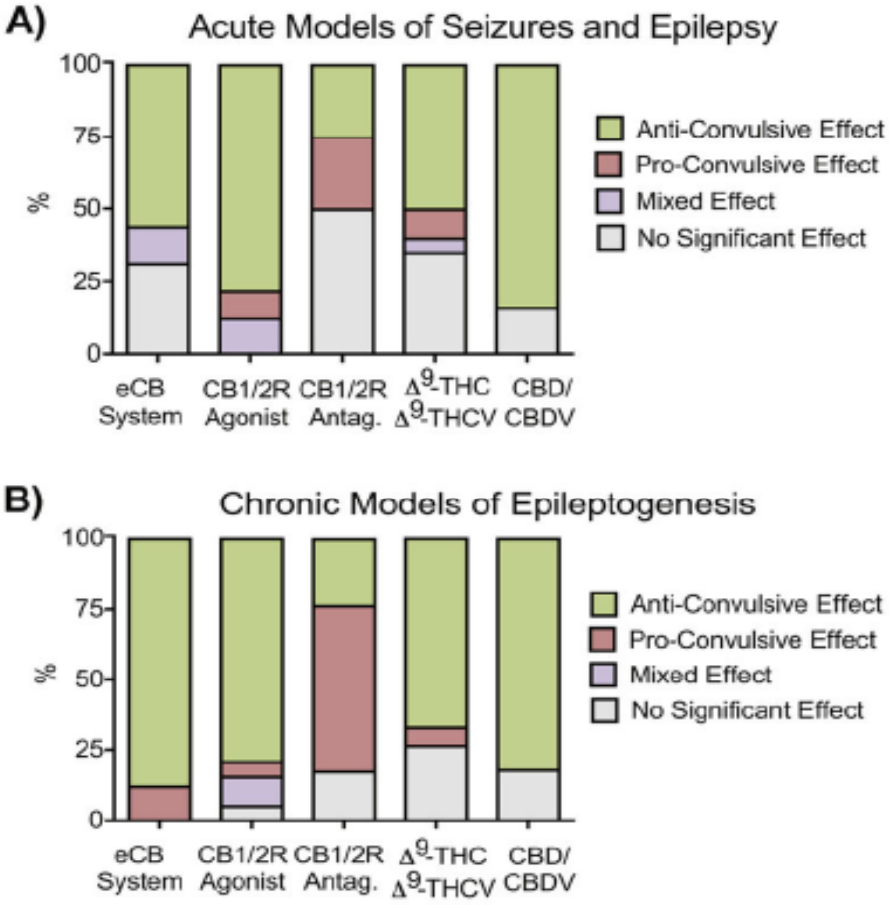
Int. J. Environ. Res. Public Health 2021, 18, 3993

Therapeutic effects of cannabinoids in animal models of seizures, epilepsy, epileptogenesis, and epilepsy-related neuroprotection.

- ECS signaling is thought →an important role in **epileptogenesis** → epilepsy.
- By regulating the biochemical synthesis and degradation of ECS (2-AG and AEA), as well as AEA reuptake→**anti-seizure effects** in pre-clinical acute models of seizure
- Both direct (i.e. CB1R agonism) and indirect approaches (inhibition of endocannabinoid catabolism) can hinder **epileptogenesis** in animal models
- Cannabinoids →**neuroprotective** candidates with seizures-induced brain injury.
  - →inhibition of excitotoxic insults
  - →inhibition of free radical-induced oxidative damage, regulation of PI3K/Akt/GSK-3 signaling pw, augmentation of microcirculation in brain +protection of the microglial function

Epilepsy Behav. 2017, 70, 319–327.

Cannabinoids & SZ, Epileptogenesis, Neuroprotection



- Pre-clinical animal models of seizures, epilepsy, and epileptogenesis. Compiled data from synthetic and phytocannabinoids in 181 total animal models of
  - A. Acute models of seizures and epilepsy.
  - B. Chronic models of epileptogenesis.
- Pre-clinical interventions were subdivided into
  - (1) Modulators of the Endocannabinoid System (“eCB”)
  - (2) CB1/CB2R Agonists,
  - (3) CB1/CB2R Antagonists,
  - (4) D9THC/THCV,
  - (5) CBD/CBDV.

Epilepsy Behav. 2017,70(Pt B): 319–327

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

Pamplona ,et al.2018

Effect	CBD purified	CBD enriched	Difference
Sz improved	36%	71%	P < 0.0001
>50 % sz reduction	42%	37%	P =NS
Sz free	~10%	~10%	P= NS
Mean dose	27.1 mg/kg/d	6.1 mg/kg/d	22.5% diff
Mild ADR	158/216, 76%	148/447, 33%	P < 0.0001
Severe ADR	41/155, 26%	23/328, 7%	P < 0.0001

Treatment references	Medical center	Study design	Patients	Age (year)	Duration
CBD pure (6)	Langone Med. Center NY Univ. (USA)	Prospective medical record	137	10.5 year (1–30)	3 months
CBD pure (7)	Child Neurology, Child Hosp. Philadelphia (USA)	Prospective medical record	7	NR	12 months
CBD pure (8)	Pediatric Epilepsy, Mass. Gen. Hospital-Harvard (USA)	Prospective medical record	13	10.8 year	2 months
CBD pure (9)	Pediatric Epilepsy, Mass. Gen. Hospital-Harvard (USA)	Prospective medical record	18		
CBD pure (10)	Langone Med. Center NY Univ. (USA)	Prospective medical record	48		
CBD-rich extract (11)	Neurology, Stanford (USA)	Parent survey (online)	19	(2–16)	
CBD-rich extract (12)	Pediatric Neurology, Univ. Calif. Los Angeles-UCLA (USA)	Parent survey (online)	117	6 year (0.4–NR)	6.8 months
CBD-rich extract (28)	Pediatrics and Neurology, Univ. Colorado (USA)	Retrospective medical record	75	7.3 year (0.5–18)	5.6 months
CBD-rich extract (13)	Pediatric Neurology, Sheba Medical Center (Israel)	Retrospective medical record	74	~10 year (1–18)	6 months
CBD-rich extract (14)	Inst. Tec. Est. Sup. Monterrey (Mexico)	Parent survey (online)	53	~9.4 year (0.8–18)	4.2 months (1–12)
CBD-rich extract (15)	Pediatrics and Neurology, Univ. Colorado (USA)	Retrospective medical record	119	7.5 year (0.1–18)	11.7 months

DATA meta-analysis :
- CBD rich : retrospective, pt survey
- CBD pure: prospective

Efficacy and safety of CBD enriched in pediatric drug resistant epilepsy in Observational Data Meta-analysis vs Thailand

Effect	CBD purified	CBD enriched	Thai CBD enriched
Total cases	223	447	14
Duration of Rx (mo)	3-12	4-12	12
Convulsive Sz improved	36%	71%	58%
>50% SR responder	42%	37%	50%
Sz free	~10%	~10%	14%
Mean dose (mg/k/d)	27.1	6.1	5.6
Mild ADR	158/216, 76%	148/447, 33%	10/14, 71%
Severe ADR	41/155, 26%	23/328, 7%	6/14, 42%
Study	*Meta-analysis Pamplona ,et al.2018*		*Retrospective Cohort Lusawat, et al 2021*

Gaps in knowledge: CBD for epilepsy in adults, long-term safety, and access to CBD

- Adult with epilepsy are underrepresented in most CBD trials : common etiologies focal epilepsy.
- Cannabis use associated with executive dysfunction →impair worker and driver safety
- Long-term cognitive, behavioral, and psychiatric side effects are another concern
- No clinical data of teratogenicity of CBD→ prenatal cannabis is associated with low birth weight
- For the same CBD plasma level, differences in seizure improvement do not depend on age
  - Plasma levels may be a strategy to guide CBD doses
- Can be defined as necessity to ↑ dose by at least 30% or a response >30%.reduction
- The mean time until the appearance of tolerance was found to be 7 months
- The long-term risks and efficacy of CBD use are unknown
- Cost is prohibitive for some patients

Front. Neurol. 2020, 11:531939

Further reading

- Highly Purifed Cannabidiol for Epilepsy Treatment : A Systematic Review of Epileptic Conditions Beyond Dravet Syndrome and Lennox–Gastaut Syndrome *CNS Drugs 2021, 35:265–281*
- Add-on Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex A Placebo-Controlled Randomized Clinical Trial *JAMA Neurol. 2021;78(3):285-292.*
- Cannabidiol in the Treatment of Epilepsy: A Focused Review of Evidence and Gaps *Front. Neurol. 2020, 11:531939*
- Receptors and Channels Possibly Mediating the Effects of Phytocannabinoids on Seizures and Epilepsy *Pharmaceuticals 2020, 13, 174*
- Phytocannabinoids other than CBD in epilepsy *Int. J. Environ. Res. Public Health 2021, 18, 3993*
- Potential Clinical Benefits of CBD-Rich Cannabis Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis *Front. Neurol.2018, 9:759*

THANK YOU

สถาบันประสาทวิทยา

Neurological Institute of Thailand

โรงพยาบาลเฉพาะทางโรคสมองและระบบประสาทไขสันหลัง