Cannabis, ”Wonder Drug” for epilepsi ?

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Februar 2016

Effektiv behandling af epilepsi ?

Ca. 40-50000 i DK, heraf ca. 5000 børn
Ca. 500 nye børnetilfælde per år

30 % af patienter har fortsat anfald trods behandling

<u>Dette har ikke ændret sig igennem mange år trods nye medikamenter</u>

Epilepsi ?

- Anfald ? Udløses af mange forskellige cellulære mekanismer
- Eller mange forskellige sygdomme ? (Genetiske epilepsier, f.eks. Dravet, metaboliske sygdomme (f.eks. Glut-1), hjernemisdannelser eller Lennox Gastaux Syndrom, ukendt årsag)
- Eller de individuelle forskelle i de epileptiske netværk ?
- Findes der ***enkle behandlinger*** til komplekse sygdomme ??

Stigende fokus på non-medikamentel behandling

- Specielle diæter, ketogen diæt, modificeret Atkins diæt, Low Glycemic Index Treatment

- Neurostimulatorer

- Neurokirurgi

- Men hvad med plantemedicin ?

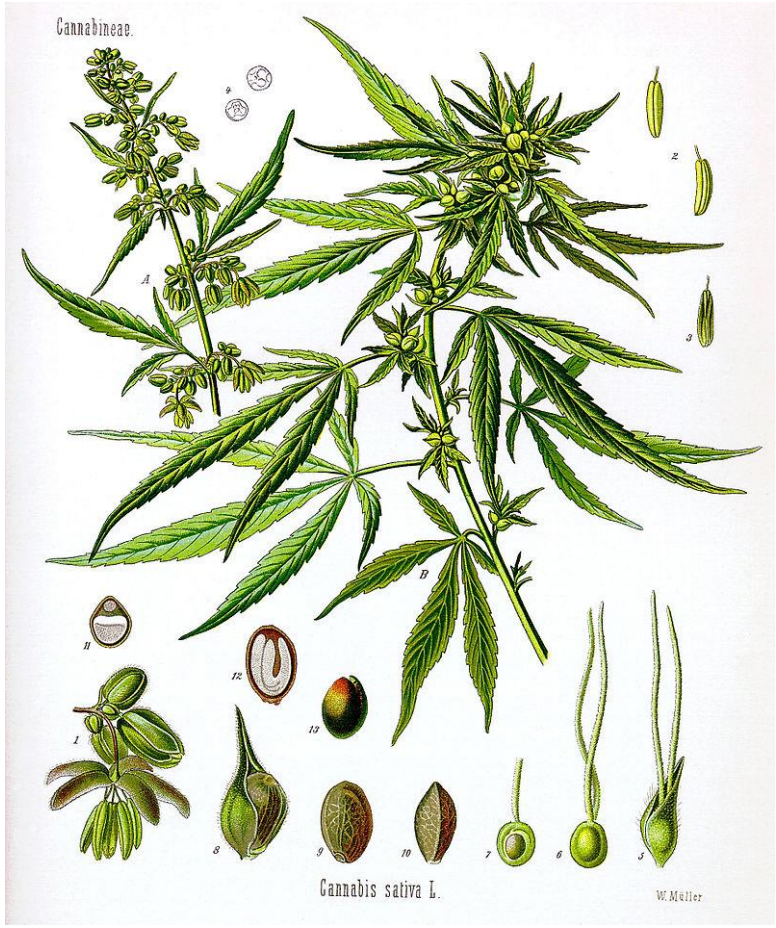
Hvad er Cannabis ?

- Etårig plante, stammer oprindeligt fra Indien

- Cannabis Sativa (alm hampeplante)
- Cannabis Indica
- Cannabis Ruderalis

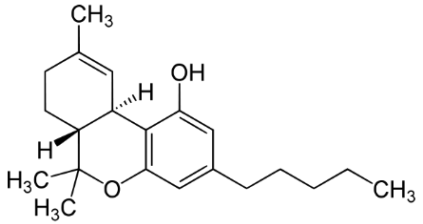
- Udbredt rusmiddel,

45% af befolkningen under 35 år har eksperimenteret med hash, og 11.000 danskere har et egentligt misbrug

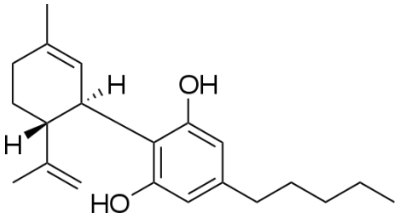


Cannabis
Over 85 forskellige Phyto-Cannabinoider

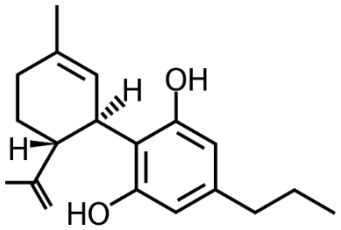
- THC (delta-9-tetrahydrocannabiol) virker smertestillende, muskelafslappende, kvalmestillende, appetitstimulerende og euforiserende. Specielt når koncentrationen stiger hurtigt i centralnervesystemet



- CBD (Cannabidiol) virker muskelrelakserende, angstdæmpende og reducere THC's psykoaktive virkning



- CBDV (Cannabidivarin) Ikke euforiserende (Cannabis Indica)



Cannabis

- hash er harpiks, der er presset og solgt i klumper
- marihuana (pot) er tørrede topskud fra C. Sativa
- skunk er marihuana, men med højere THC-indhold, der er opnået ved planteforædling
- cannabisolie er en tyktflydende olie, der er presset eller ekstraheret fra hash

Cannabisbivirkninger

- Angst-panikreaktioner
- Psykotiske reaktioner (hash-psykoser)
- Ved Cannabis kan der ikke forekomme dødelige overdoser i forhold til manglende vejrtrækning
- Hurtig puls, lavt blodtryk, slimhindeirritation, muskelslaphed og forstoppelse
- Hjernen udvikler en tolerance til cannabinoider, ved pludselig ophør kan ses irritabilitet, søvnforstyrrelser, rastløshed, udslæt, kvalme

Cannabisbivirkninger vedr. THC

- Stærk mistanke om alvorlige langtidsbivirkninger på både kort og langtidshukommelse
- Reducerede eksekutive funktioner herunder opmærksomhed
- Skadelig påvirkning af den neuronale plasticitet specielt på hjerner i udvikling

- Trezza V, Cuomo V, Vanderschuren LJMJ.. Cannabis and the developing brain: Insights from behavior. Eur J Pharmacol 2008;585:441-52.
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Omsætningen i kroppen

Ved peroral indtagelse af Cannabis: Max uptake 1-6 timer, halveringstid i kroppen 20-30 timer, omdannes i leveren til et meget psykoaktivt stof 11-OH-THC

Ved rygning max koncentration efter ca. 10 min, hurtig udskillelse og mindre dannelse af 11-0H-THC

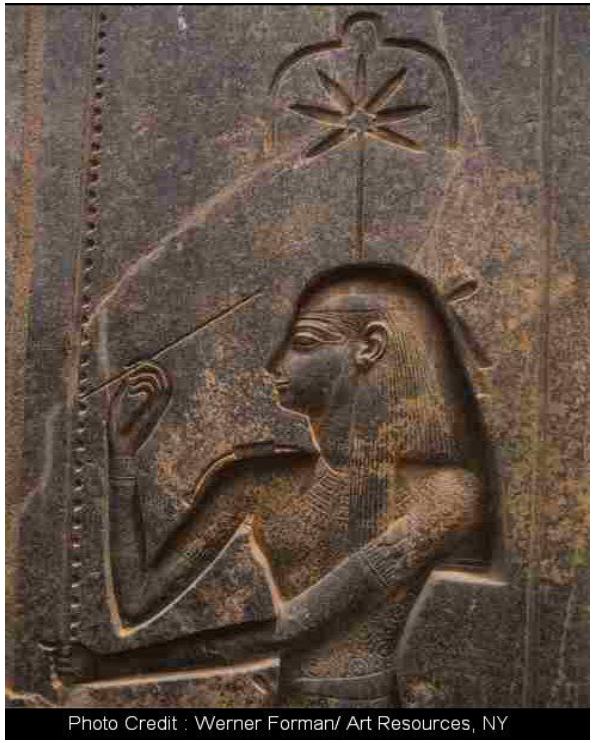
Ved kronisk indtagelse ophober sig i fedtvæv og udskilles langsomt, halveringstid ca. 1-3 dage

Kan vi få inspiration til epilepsibehandling ved at gå tilbage i tiden ?

- Kaliumbromid, det første kendte antiepileptiske middel fra 1857. Nu opstartet ved Epilepsihospitalet til Dravet Syndrom
- Fenemalbehandling fra 1912, bruges fortsat til akut og fast behandling
- Nervus Vagus behandling. I oldtiden blev vagusstimulation på halsen brugt som anfaldsbehandling
- Ketogen diæt, opstarter i 1920´erne, tiltagende udbredelse igennem de senste 15 år

Ikke en ny ide at behandle med Cannabis !

- 650 f.KR:, Assyrien: Første skrevne dokumenteret brug af ”medicinsk”cannabis (British Museum of London)
- 1100 e.KR: (al-Mayusi), 1400 e.KR: (al-Badri): Alm. brug af cannabis for epilepsi tillige med nasal administration.



ON THE PREPARATIONS

OF THE

INDIAN HEMP, OR GUNJAH

(CANNABIS INDICA);

THEIR EFFECTS ON THE ANIMAL SYSTEM IN HEALTH, AND THEIR UTILITY IN THE TREATMENT OF TETANUS AND OTHER CONVULSIVE DISEASES

By W. B. O'Shaughnessy, M.D.,

Assistant-Surgeon, and Professor of Chemistry, &c.

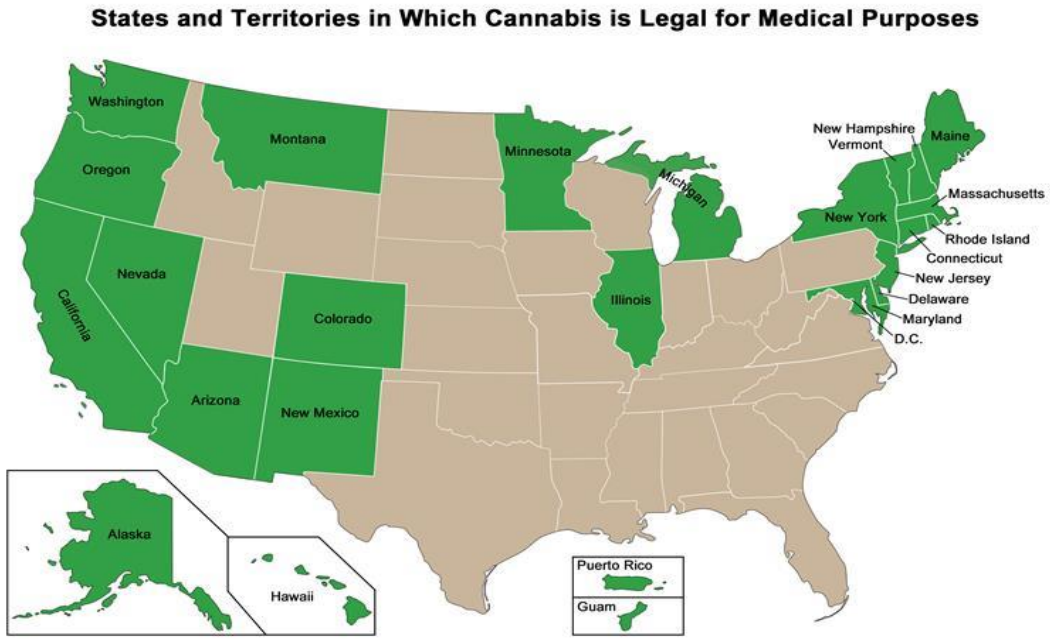
In the Medical College of Calcutta.

Presented October, 1839.

Sir John Russell Reynolds, (22 May 1828 – 29 May 1896)
Dronning Victoria's livlæge, "*I have found hemp very useful*" for treating epilepsy

Cannabis i USA

- 1851: US Dispensary (apoteker): Cannabis sælges for nervesmerter, depression, kramper, psykiske problemer
- 1860: Ohio Medical Society anbefaler Cannabis for epilepsi og andre sygdomme
- 1911: Massachusetts: 1. stat i US der forbyder cannabis
- 1970: US Controlled Substances Act: ”No accepted medical use”
- 1996: Californien er den første stat der legaliserer medicinsk marihuana
- 2015: Medicinsk marihuana legaliseret i 23 US stater, CBD er endvidere legalt i yderligere 16 stater



Behandling med medicinsk cannabis
Media *Hype*

- Enorm omtale, tusinder af artikler, FACEBOOK

- Dr Sanja Gupta (neurokirurg) positive omtale om behandlingsmulighederne:
  Sanjay Gupta Says It's Time For A Medical Marijuana 'Revolution'
  Apr 17, 2015

- Placebo-respons: Normalt i forsøg fra 9-15 %

- Forstærkes ved positive forventninger, de negative erfaringer omtales sjældent

Marijuana stops child's severe seizures

By Saundra Young, CNN

Updated 2151 GMT (0451 HKT)
August 7, 2013

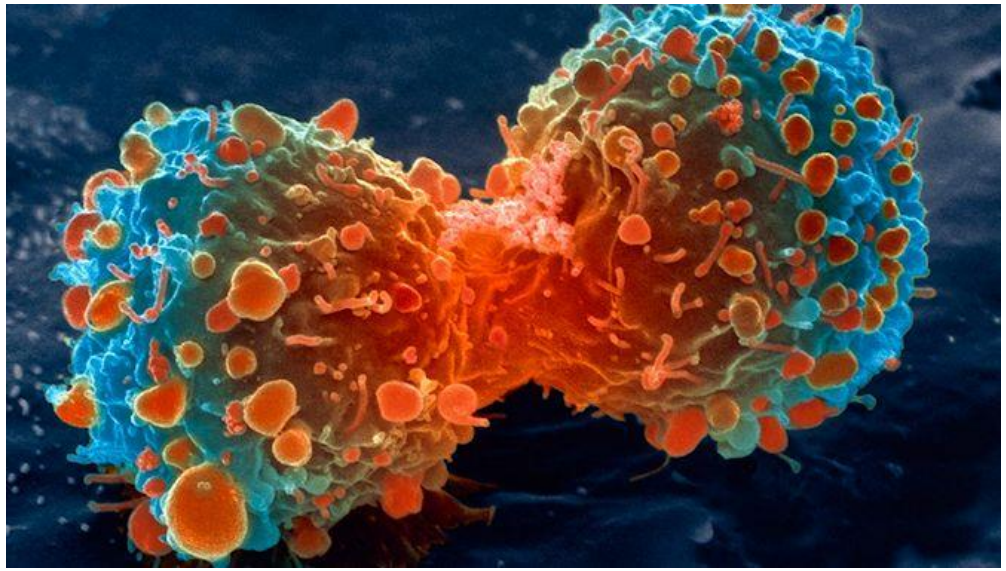
Hvis Cannabis virker mod epilepsi, hvad er forklaringen ??

- Kan vi få tilført viden fra behandling af andre lidelser ?
- Giver virkningsmekanismen mening i forhold til epilepsi ??
- Resultaterne af dyreforsøg ?
- Hvordan er de kliniske data ?

Cannabis og cancer

- Medicinsk cannabis brugt i AIDS behandling siden 1986 (Dronabinol)
- Virker appetitstimulerende, reducerer smerter, reducere kvalme og giver bedre søvn
- Dyreforsøg: Antitumor effekt, antiinflammatorisk

(NIH, National Cancer institut)



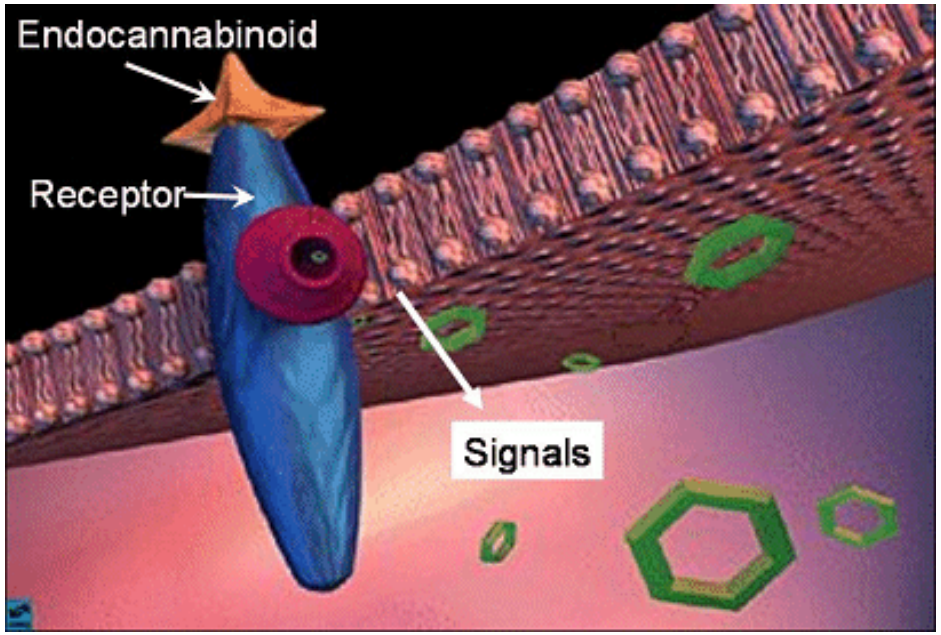
Kroppen har sit eget ”Cannabissystem” Det Endocannabinoide System:

- Smertemodulering
- Social adfærd/angst
- Hukommelse
- Søvnregulering
- Stressrespons
- Immunmodulation
- Autonome nervesystem
- Energibalance og metabolisme
- Inflammation
- Regulering af temperatur
- Fødeindtag
- Graviditet (det befrugtede ægs evne til at implantere sig)

Cannabisreceptor

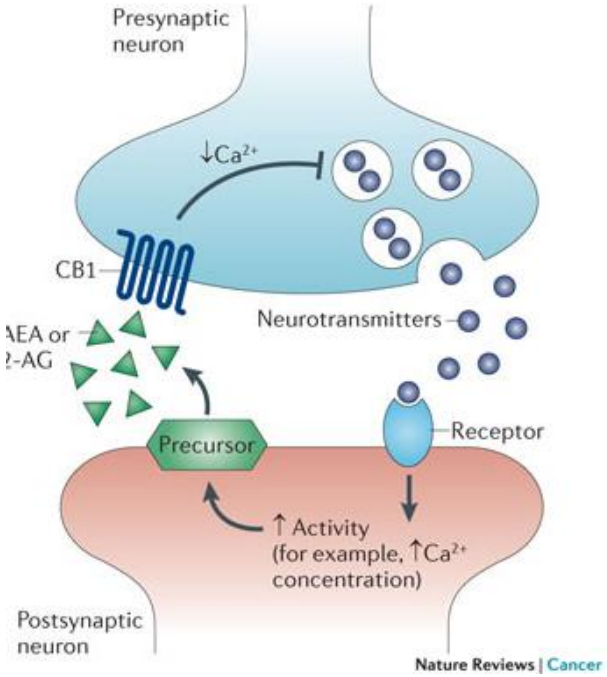
- CB-1-receptor er lokaliseret primært i hjernen (hippocampus, basal ganglier og cerebellum (1998)) men også i det perifere nervesystem. Desuden hjerte, mavetarm, reproduktionsorganer
- CB-2-receptor: Findes primært i immunsystemet (1993), men også i pancreas, tarm, retina
- GPR 55
- TRPV type 1

<u>THC binder sig til CB1 og CB2, men CBD binder sig meget lidt !!!</u>



Endocannabinoider: ”Signalstoffer” der aktiverer receptorerne.

- 2AG (arachidonoylglycerol)
- AEA (Anandamid)



Lipid signalmolekyler

Dannes fra cellemembranen

Binder til receptoren i cellemembranen

Hurtig syntese, aktivering og nedbrydning

Funktion: Åbning af kaliumkanaler, lukning af calciumkanaler, hæmmer frigørelsen af signalstoffer og dermed reducere transmissionen over synapsen ved intens aktivitet

https://www.youtube.com/watch?v=jznQfMj9RWM

Hvilke virkningsmekanismer i forhold til epilepsi ?

- Antiinflammatorisk ?
  (Nogle epilepsiformer som CSWS, Rasmussens syndrom behandles med immunhæmmende behandling som steroider)
- Ved stimulation af CB-1-receptorer nedsat præsynaptisk afgivelse af glutamat (Glutamat er et signalstof der kan medføre øget fyring fra nerveceller, medicin som Fycompa virker dæmpende på Glutamatsystemet). Desuden reduceres frigivelse af blandt andet Noradrenalin og Dopamin
- Aktiverer 5 HT 1A receptorer
  (Findes i mange hjerneafsnit, del af de serotonerge nervesystem, betydning for depression og angst. Dyreforsøg har vist krampedæmpende effekt. Stimulation af systemet (Buspiron) bruges ved angst
- Hæmmer Adenosin reuptake
  Kroppens eget krampemedicin, betydning for anfaldsophør og den post-iktale periode. Forskning pågår vedr. medicinsk udvikling men desværre udtalte bivirkninger

Hvad har dyremodellerne vist ?

- Siden 1970 er CBD blevet afprøvet på en lang række af dyremodeller

- Akutte anfaldsmodeller med god effekt, kroniske anfaldsmodeller med mindre overbevisende
  (Devinsky et al, Epilepsia 2014)

- THC kan udløse kramper
  (Karler R, Calder LD, Turkanis SA.. Prolonged CNS hyperexcitability in mice after a single exposure to delta-9-tetrahydrocannabinol. Neuropharmacology 1986;25:441-6.)

Tidligere kliniske forsøg

Til for 5 år siden 4 publiserede forsøg, ialt 70 personer, lav evidens for effect

- Udviklingen tog fart efter:
- Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

Brenda E. Porter and Catherine Jacobson Epilepsy Behav. 2013 Dec; 29(3): 574–577

- 19 patienter, CBD. Selvrapportering
- Thirteen children had Dravet syndrome, four had Doose syndrome, and one each had Lennox-Gastaut syndrome and idiopathic epilepsy. The average number of anti-epileptic drugs (AEDs) tried before using cannabidiol-enriched cannabis was 12. Sixteen (84%) of the 19 parents reported a reduction in their child's seizure frequency while taking cannabidiol-enriched cannabis. Of these, two (11%) reported complete seizure freedom, eight (42%) reported a greater than 80% reduction in seizure frequency, and six (32%) reported a 25-60% seizure reduction

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

Tzadok M[1] Seizure. 2016 Jan 6;35:41-44. doi: 10.1016/j.seizure.2016.01.004.

- **METHODS**

A retrospective study describing the effect of cannabidiol (CBD)-enriched medical cannabis on children with epilepsy.

The cohort included 74 patients (age range 1-18 years) with intractable epilepsy resistant to >7 antiepileptic drugs. Forty-nine (66%) also failed a ketogenic diet, vagal nerve stimulator implantation, or both. They all started medical cannabis oil treatment between 2-11/2014 and were treated for at least 3 months (average 6 months). The selected formula contained CBD and tetrahydrocannabinol at a ratio of 20:1 dissolved in olive oil. The CBD dose ranged from 1 to 20mg/kg/d. Seizure frequency was assessed by parental report during clinical visits

- **RESULTS**

CBD treatment yielded a significant positive effect on seizure load. Most of the children (66/74, 89%) reported reduction in seizure frequency:

18% reported 75-100% reduction,

34%reported 50-75% reduction,

12% reported 25-50% reduction

7% patients reported aggravation of seizures which led to CBD withdrawal.

In addition, we observed improvement in behavior and alertness, language, communication, motor skills and sleep.

Adverse reactions included somnolence, fatigue, gastrointestinal disturbances and irritability leading to withdrawal of cannabis use in 5 patients

Epidiolex, GW Pharma (UK)
Expanded Access Program (EAP)

- Epidiolex klassificeret som ”Orphan Drug” af FDA, Aktuel tilladelse til ”Fast-Tracking” med henblik på hurtig undersøgelse af effekten.
- **Orphan drug** er et lægemiddel der er udviklet til at behandle sjældne medicinske sygdomme (Orphan disease).
- EAP: Program for patienter der ikke har haft mulighed for at indgå i de kliniske afprøvninger og som mangler behandlingsmæssige alternativer
- I alt 870 børn og unge med behandlingsresistent epilepsi har afprøvet Epidiolex

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial.

Devinsky O[1] et al Lancet Neurol. 2015 Dec 23

- **METHODS**

In this open-label trial, patients (aged 1-30 years) with severe, intractable, childhood-onset, treatment-resistant epilepsy, who were receiving stable doses of antiepileptic drugs before study entry, were enrolled in an expanded-access programme at 11 epilepsy centres across the USA. Patients were given oral cannabidiol at 2-5 mg/kg per day, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day (dependent on study site). The primary objective was to establish the safety and tolerability of cannabidiol and the primary efficacy endpoint was median percentage change in the mean monthly frequency of motor seizures at 12 weeks.

RESULTS

Between Jan 15, 2014, and Jan 15, 2015, 214 patients were enrolled;

162 (76%) patients who had at least 12 weeks of follow-up after the first dose of cannabidiol were included in the safety and tolerability analysis,

and 137 (64%) patients were included in the efficacy analysis. In the safety group, 33 (20%) patients had Dravet syndrome and 31 (19%) patients had Lennox-Gastaut syndrome. The remaining patients had intractable epilepsies of different causes and type.

Adverse events were reported in 128 (79%) of the 162 patients within the safety group. Adverse events reported in more than 10% of patients were somnolence (n=41 [25%]), decreased appetite (n=31 [19%]), diarrhoea (n=31 [19%]), fatigue (n=21 [13%]), and convulsion (n=18 [11%]). Five (3%) patients discontinued treatment because of an adverse event. (12%) patients had severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]).

The median reduction in monthly motor seizures was 36·5% (IQR 0-64·7)

Cannabidiol Treatment of Refractory Epileptic Spasms: An Open-Label Study

Abati E, Hess E, Bruno P, Thiele EA
The Herscot Center for Tuberous Sclerosis Complex and Pediatric Epilepsy Program
Massachusetts General Hospital

INTRODUCTION

Epileptic spasms is an epileptic syndrome of infancy and childhood. It is defined as an epileptic encephalopathy, a condition in which the epileptic activity contributes to progressive brain dysfunction.[1]

The prognosis of epileptic spasms may be severe. Neurodevelopmental disabilities and chronic epilepsy are common, with 70-90% of patients showing cognitive impairment, and 50% of children developing intractable seizures.[1,2] The persistence of seizures worsens neurodevelopmental outcomes; therefore it is important to recognize and treat epileptic spasms early and aggressively.[1]

This study evaluates the safety and tolerability of cannabidiol (CBD), a non-psychoactive cannabinoid present in the marijuana plant, in treating refractory epileptic spasms.

METHODS

A current IRB and FDA approved clinical trial at Massachusetts General Hospital (MGH) is studying the use of CBD as adjunctive treatment for refractory epilepsy under an expanded access IND. We selected nine patients with a diagnosis of treatment-resistant epileptic spasms among the cohort enrolled in the trial.

Seizure frequency, intensity, and duration were measured during a baseline period of at least 28 days. Patients were started on CBD at a dosage of 5 mg/kg/day, and were increased by 5 mg/kg/day weekly up to a maximum dose of 50mg/kg/day. Patients were seen in our clinic biweekly to monthly and reported seizure frequency, intensity, and duration.

Response rates (percentage of patients with a greater than 50% reduction in seizures) were calculated, and side effects were recorded over the course of 1,2,3,6,9 and 12 months of CBD treatment. Subjective cognitive and behavioral changes by parent report were noted.

RESULTS

Table 1. Demographics and Epilepsy History

Case	Sex	Age	Underlying Conditions	Age at Spasms Onset	Concomitant AEDs	Side Effects
1	M	14	dup15q13	6 mo	VPA, LVT, CLB	Drowsiness, ataxia, appetite loss, elevated LFTs
2	M	16	Bilateral cerebral dysgenesis	4 mo	VGB, ZNM, CLB	Drowsiness
3	F	10	Lissencephaly	4 mo	CLB, LVT, RFN	Drowsiness, diarrhea
4	M	5	*SCN2A*	9 mo	LCS, CLB, TPM, LVT	Drowsiness, twitchiness
5	F	2	Unknown	4 mo	TPM, VGB, CLB	None
6	M	8	TSC	4 mo	LCS, LVT, CLB	Drowsiness, ataxia, appetite loss, agitation
7	F	13	TSC	6 mo	LCS, CLB, VPA	Drowsiness
8	F	3	TSC	16 mo	LVT, CLB	Agitation
9	F	8	*CASK* LoF	21 mo	VGB, CLB, LCS	Drowsiness, irritability

AEDs = antiepileptic drugs, VPA = valproic acid, LVT = levetiracetam, CLB = clobazam, VGB = vigabatrin, ZNS = zonisamide, RFN = rufinamide, LCS = lacosamide, TPM = topiramate, LTG = lamotrigine, LoF = loss of function, TSC = tuberous sclerosis complex

Table 2: Change in Seizure Frequency and Response

	Case	2 weeks	1 mo	2 mo	3 mo	6 mo	9 mo	12 mo
Individual changes in spasm frequency	1	-74%	-84%	-35%	-22%	-76%	+80%	+163%
	2	-100%	-94%	-82%	-61%	-69%	-86%	-85%
	3	-100%	-100%	-100%	-100%	-100%	-100%	-100%
	4	-100%	-97%	-100%	-100%	-100%	-100%	N/A
	5	+11%	+11%	+10%	+12%	-30%	N/A	N/A
	6	-95%	-94%	-76%	-75%	-80%	N/A	N/A
	7	-99%	-92%	-100%	-100%	-100%	N/A	N/A
	8	-15%	-4%	-58%	-49%	N/A	N/A	N/A
	9	-34%	-58%	-38%	N/A	N/A	N/A	N/A
Response Rates		67%	78%	67%	63%	85%	75%	67%
Mean Change in Seizure Frequency		-67%	-68%	-64%	-62%	-79%	-51%	-7%

SUMMARY/CONCLUSIONS

- Epileptic spasms often remain refractory to standard anti-epileptic drugs, thus there is a need for new, effective, and safe medications.
- CBD exerted its effects in a short time course, with a response rate of 67% after two weeks and 78% after 1 month. Three of nine patients became spasm-free after two weeks of CBD treatment..
- By parent report, patients showed cognitive gains including improvements in alertness, verbal capacity/communication, and cognitive availability.
- Diarrhea was the only side effect noted to be directly attributed to CBD. Other adverse events such as drowsiness, ataxia, appetite loss, agitation, irritability, and elevated LFTs were the result of drug-drug interactions, which occurred in eight patients. These side effects were alleviated by AED dose adjustments without loss of seizure control.
- Other calculated response rates (table not depicted here) show that CBD is effective at dosages as low as 10 mg/kg/day and can be safely increased to 50 mg/kg/day.
- Further study of CBD treatment in patients with refractory epileptic spasms are indicated in order to increase statistical significance. However, these findings suggest that CBD is a safe, well-tolerated, and effective treatment option for epileptic spasms.

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2. Wong M, Trevathan E. Infantile spasms. Pediatr Neurol. 2001;24:89–98.

ACKNOWLEDGEMENTS

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Cannabidiol (CBD) Treatment for Refractory Epilepsy in Tuberous Sclerosis Complex (TSC)

Geffrey AL, Pollack SF, Hess EJ, Paolini JL, Bruno PL, Thiele EA
The Herscot Center for Tuberous Sclerosis Complex and Pediatric Epilepsy Program
Massachusetts General Hospital

MassGeneral Hospital for Children

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder, characterized by benign hamartomas in various organs, including the brain, heart, lungs, skin, eyes, and kidneys.[1] TSC results from a mutation in tumor suppressor genes *TSC1* or *TSC2*, leading to aberrant regulation of the mammalian target of rapamycin (mTOR).

The most common symptom of TSC is epilepsy, which occurs in 75-90% of patients; approximately 70% of these patients experience seizure onset in their first year of life and most experience multiple seizure types.[2,3] Refractory epilepsy is a serious condition that is twice as common in the TSC population than in the general epilepsy population.[3]

This study explores cannabidiol (CBD) as a possible treatment of refractory epilepsy in TSC.

METHODS

Under an expanded access IND from the FDA, we are conducting a trial to determine the safety, tolerability, as well as efficacy of CBD (Epidiolex, GW Pharma) as an adjunctive treatment in children and young adults with drug-resistant epilepsy.

Ten patients in the study have a refractory epilepsy in the setting of TSC. Data collected from the study were reviewed for demographics, epilepsy history, genetic analysis, and behavioral and cognitive issues. Cognitive impairment was defined by an IQ of <70. Cognitive and behavioral changes were based on parental report and/or clinician observation. Subjects were classified as responders if they showed greater than 50% decrease in seizure frequency after 16 weeks of treatment (including a 5 week titration of 5 mg/kg/day up to 25 mg/kg/day). Baseline seizure frequencies were measured for four weeks immediately preceding initiation of CBD treatment.

RESULTS

Table 1. Overview of TSC cases treated with CBD

Case	Sex	Age	Mutation	Age at Seizure Onset	History of Spams	Responder
1	M	13	TSC1	5 y/o	no	yes
2	M	5	TSC1	1 mo	no	yes
3	M	16	Unknown	6 y/o	yes	yes
4	M	14	TSC2	8 mo	yes	no
5	F	11	TSC2	3 mo	yes	no
6	M	2	TSC1	3 mo	yes	no
7	F	8	Unknown	5 mo	no	yes
8	M	8	TSC2	4 mo	yes	no
9	F	12	TSC2	1 mo	yes	yes
10	M	22	Unknown	4 y/o	no	yes

Table 2. History of AEDs and other epilepsy treatments, seizure types, and side effects experienced during treatment with CBD

Case	Seizure Types	Concomitant AEDs	Number of Past AEDs	Other Treatments	Side Effects
1	FD	LTG, CLB	8	None	none
2	FD, T, ABS	LCS, CLB, LZP	8	None	diarrhea, irritability
3	FD, FD 2°, A	LTG, LCS, PHT, LZP	7	VNS	diarrhea, drowsiness
4	FD	LTG, LCS	9	Diet	none
5	FD, FD 2°	LCS, VPA, DZP	7	VNS	none
6	FD	LEV, LCS	3	Diet	none
7	FD	LCS	9	None	none
8	T, FD, S	LCS, LEV, CLB	4	Diet	drowsiness
9	TC, T, A, ABS, S	CLB, VPA, LCS	7	Epi. surgery	drowsiness
10	FD, TC	CLB, LCS	5	None	drowsiness

AEDs = antiepileptic drugs, LTG = lamotrigine, CLB = clobazam, LCS = lacosamide, LZP = lorazepam, VPA = valproic acid, DZP = diazepam, VNS = vagus nerve stimulator, FD = focal dyscognitive, T = tonic, ABS = atypical absence, 2° = with secondary generalization, A = atonic, S = spasm, TC = tonic clonic, epi. = epilepsy.

SUMMARY/CONCLUSIONS

- All seizure types responded to CBD treatment in some patients, including in overall non-responders.
- Patient 9 became seizure free after 2 months of CBD treatment and has remained seizure free for the past 10 months.
- By parent report, patients 1, 2, and 4 to 9 showed cognitive gains including improvements in alertness, verbal capacity/communication, vocalizations, cognitive availability, and initiation of emotional and physical connections.
- Responder rate data reflects 16 weeks of treatment. Some patients appear to be late responders, and data regarding this as well as maintenance of response is currently being analyzed.
- Diarrhea was the only side effect noted to be directly attributed to CBD. Other adverse events such as drowsiness and irritability were the result of drug-drug interactions, which occurred in five patients. These side effects were alleviated by AED dose adjustments without loss of seizure control.
- Refractory epilepsy occurs frequently in TSC. Although additional studies are needed, the data in this small population suggests that CBD is safe, well-tolerated, and effective, thus expanding treatment options for refractory epilepsy in patients with TSC.

REFERENCES

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ACKNOWLEDGEMENTS

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Klinisk afprøvning

- Fase II udføres på en større gruppe patienter der lider af den sygdom medikamentet er rettet imod (20-300) for at undersøge hvor effektivt det er til at behandle sygdommen i forhold til forskellige doser, samt dets bivirkningsprofil
- Fase III udføres på en meget stor gruppe patienter (typisk 300-3000) for at give en endegyldig vurdering af behandlingens virkning. Fase III-undersøgelser er i sagens natur forholdsvis dyre og tidsforbrugende. På basis af fase III-undersøgelsen kan lægemidlet blive godkendt af myndighederne
- Randomiseret blindet forsøg

PRE-CLINIC
PHASE 1
PHASE 2
PHASE 3
SUBMIT
APPROVAL
Unpartnered – GW owns global rights
EPILEPSY
EPIDIOLEX
DRAVET SYNDROME
2 PHASE 3 TRIALS UNDERWAY
EPIDIOLEX
LENNOX-GASTAUT SYN.
2 PHASE 3 TRIALS UNDERWAY
EPIDIOLEX
TUBEROUS SCLEROSIS
PHASE 3 TRIAL TO COMMENCE H2 2015
GWP42006 (CBDV)
EPILEPSY
PHASE 2 TRIAL UNDERWAY
OTHER ORPHAN CANDIDATES
GWP42003 (I.V.)
NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY
ORPHAN DRUG DESIGNATION RECEIVED
GWP42002 GWP42003
GLIOMA
OTHER PIPELINE CANDIDATES
GWP42004
TYPE 2 DIABETES
GWP42003
SCHIZOPHRENIA
SATIVEX
Partnered
SATIVEX
CANCER PAIN
PHASE 3 TRIALS ONGOING
SATIVEX
MS SPASTICITY
PHASE 3 IND OPEN, SPA ONGOING

One of the Largest Clinical Development Programs for Seizures Associated with Dravet Syndrome or LGS Will Evaluate the Efficacy and Safety Profile of Cannabidiol (CBD)

GW pharmaceuticals

Investigating the Potential of Cannabidiol to Treat Rare, Severe Forms of Epilepsy

Dravet Syndrome and Lennox-Gastaut Syndrome (LGS) are two rare, extremely debilitating epilepsy syndromes that begin in infancy or early childhood.[1,2] GW Pharmaceuticals has partnered with leading pediatric and adult epilepsy clinicians to undertake one of the largest clinical development programs in Dravet Syndrome and LGS, studying its investigative cannabidiol product, Epidiolex (CBD). CBD is a type of cannabinoid shown in pre-clinical studies to exhibit anti-seizure and anti-inflammatory properties. The program includes four pivotal clinical trials and a large expanded access program, which will take place at many sites across the U.S. and globally and enroll more than 1,000 patients, the majority of whom are children.

PIVOTAL CLINICAL TRIAL PROGRAM

4 Randomized, blinded, Phase 3 controlled clinical trials

+

~50 Leading epilepsy investigators across the U.S.

+

>500 Patients with Dravet Syndrome or LGS

=

Largest global pivotal clinical trial program to date in Dravet Syndrome

Second largest global pivotal clinical trial program to date in LGS

Dravet Syndrome

2 Randomized, blinded, Phase 3 controlled clinical trials

=

Participants: Patients range from 2 through 18 years old with Dravet Syndrome that is not completely controlled by anti-epileptic drugs

Primary endpoint: Percentage change from baseline in convulsive seizure frequency during the treatment period (14 weeks) vs. placebo

Lennox-Gastaut Syndrome

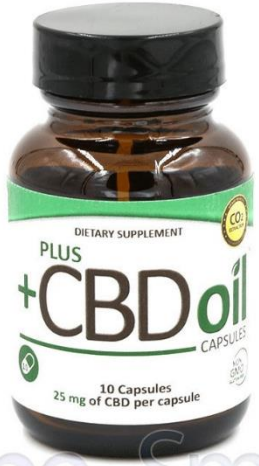
2 Randomized, blinded, Phase 3 controlled clinical trials

=

Participants: Patients range from 2 through 55 years old with evidence of at least one type of generalized seizure, including drop seizures, for at least six months

Primary endpoint: Percentage change from baseline in number of drop seizures (average per week) during the treatment period (14 weeks) vs. placebo

Påvirkning af epilepsimedicin



Hæmmer leverens cytochrom P-450 (CYP2C19):

- Frisium øges med faktor 0-30 % men Frisium metabolit (Desmetyl-clobazam) med 5-10 gange

Andre præparater:

- Lamotrigen, Lacosamid, Felbamat, Levetiracetam og formentlig endnu flere

Medicinsk Cannabis: Sativex

Mundhulespray, opløsning. 1 ml indeholder 27 mg THC tetrahydrocannabinol og 25 mg CBD. Mundhulespray 3 x 10 ml, kr 5.160,50

Indikation:

- Behandling med henblik på symptomforbedring hos patienter med moderat til svær spasticitet på grund af multipel sklerose

Forsigtighed ved:

- Alvorlig kardiovaskulær sygdom
- Epilepsi
- Krampeanfald i anamnesen.

Pludselig seponering kan medføre abstinenssymptomer, der dog oftest er milde

Lovgivning: Notat fra SST 2015.

Regler ved Cannabis som euforiserende stof:

- ”Lov om euforiserende stoffer og bekendtgørelse om euforiserende stoffer” (liste A til E)
- Slægten Cannabis tilhører liste A, må ikke findes i DK medmindre SST har givet særlig tilladelse
- Liste A: Alle ”overjordiske” dele af planten tilhørende slægten Cannabis, hvorfra harpiksen ikke er fjernet
  Undtaget er dog hampefrø og hampetaver

Lovgivning

- I § 2, stk. 3, er der en særlig regel om tilberedninger af *Cannabis*, der gør det muligt for Lægemiddelstyrelsen at give medicin en markedsføringstilladelse, der indeholder tilberedninger af *Cannabis*
- Bestemmelsen giver ikke fri mulighed for at fremstille, besidde, indføre eller anvende *Cannabis* generelt, da en række andre regler gælder ved siden af, herunder kravene i bekendtgørelse om euforiserende stoffer og om at medicin i Danmark skal have en markedsføringstilladelse eller en udleveringstilladelse fra Lægemiddelstyrelsen efter lægemiddelloven. Bestemmelsen kræver desuden, at en læge har ordineret et lægemiddel, der indeholder tilberedninger af *Cannabis* (medicinsk øjemed)

Lovgivning

- Det betyder derfor, at det er ulovligt at besidde, købe, sælge, ind- og udføre, forarbejde, anvende og udlevere *Cannabis* uden tilberedning – uanset om det måtte være ordineret af en læge
- Det er altså strafbart, hvis man eksempelvis besidder, køber, sælger, ind- og udfører, forarbejder, anvender, udleverer produkter, der indeholder tilberedninger af *Cannabis*, med mindre en læge har ordineret det og det er lovligt udleveret. En virksomhed kan dog med passende tilladelser og import- og eksportcertifikater lovligt importere, lagerføre og engrosforhandle medicin med *Cannabis*, herunder fx Sativex®
- Stoffet CBD i sin rene form er ikke omfattet af bekendtgørelsen om eufo-riserende stoffer

Lovgivning: Notat ved SST, 2015

- **Indførsel af *Cannabis* til medicinsk brug fra Holland og andre Schengen-lande**
- Hvis en person lovligt har fået en recept fra en læge, og derefter lovligt har fået udleveret tilberedninger af *Cannabis* til medicinsk brug til højst 30 dages personligt forbrug på et apotek i Holland, eller et andet Schengenland, så opfylder det kravene til at blive indført i Danmark. Det gælder eksempelvis, hvis en person har fået recept på og udleveret Sativex® …….. og indfører det til Danmark

100% NATURAL PRODUCT
MEDICINAL USE ONLY
CBD-OLIE.DK
Hampen kommer fra 100 % økologiske farme i Danmark