EPILESSIA E CANNABIS
STUDI CLINICI

Tiziana Granata
IRCCS Besta, Milano

FONDAZIONE I.R.C.C.S.
ISTITUTO NEUROLOGICO CARLO BESTA

Italia. Lega Epilessia: studiare la cannabis "senza pregiudizi"

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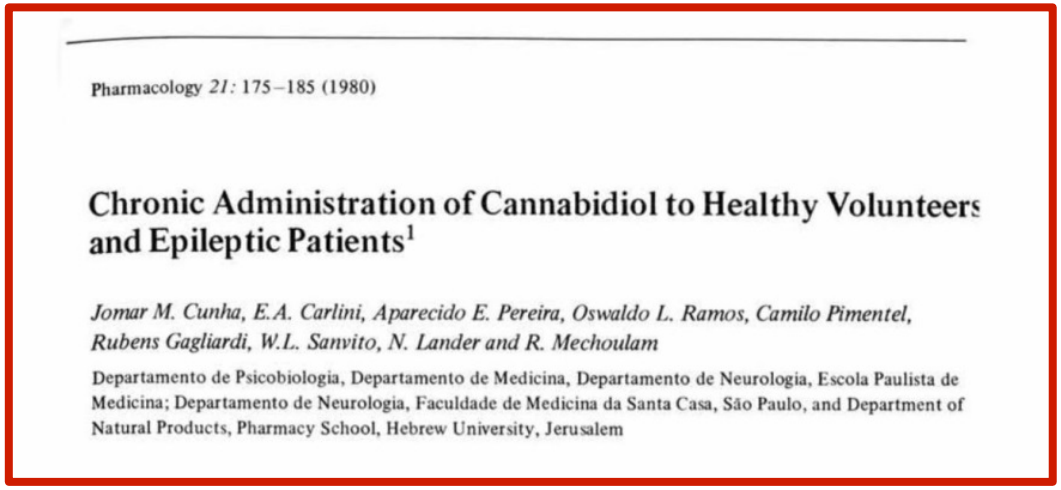
Notizia 21 maggio 2005 15:24

Cannabis, solo uno stupefacente o anche un medicinale? Sulla possibilita' di studiare l'impiego in medicina di questa sostanza si sono trovati d'accordo, pur partendo da convinzioni opposte due ricercatori, **Giovanni Ambrosetto**, associato del Dipartimento di Scienze Neurologiche dell'Universita' di Bologna e **Franco Lodi** dell'Universita' di Milano, che ne hanno parlato ieri a Bari nel corso del 28/o Congresso nazionale della Lega italiana contro l'epilessia.



Pharmacology 21: 175–185 (1980)

Chronic Administration of Cannabidiol to Healthy Volunteers and Epileptic Patients[1]

Jomar M. Cunha, E.A. Carlini, Aparecido E. Pereira, Oswaldo L. Ramos, Camilo Pimentel, Rubens Gagliardi, W.L. Sanvito, N. Lander and R. Mechoulam

Departamento de Psicobiologia, Departamento de Medicina, Departamento de Neurologia, Escola Paulista de Medicina; Departamento de Neurologia, Faculdade de Medicina da Santa Casa, São Paulo, and Department of Natural Products, Pharmacy School, Hebrew University, Jerusalem

Studio randomizzato doppio cieco: CBD contro placebo (add on)
15 pazienti con crisi secondariamente generalizzate da «temporal focus»

200-300 mg/die per 4 mesi

+ CBD

4/8 «almost seizure free»
3/8 «partial improvement»
1/8 «ineffective»

+ PLACEBO

7/8 «unchanged»
1/8 «clearly improved»

Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane Database of Systematic Reviews 2014

DOI: 10.1002/14651858.CD009270.pub3.

Cannabinoids for epilepsy (Review)

Gloss D, Vickrey B

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OUTCOME PRIMARI

proporzione di pazienti liberi da crisi (Kwan, 2010)

Nessuno studio informazioni per rispondere

OUTCOME SECONDARI

Proporzione di pazienti con riduzione crisi >50% >6 mesi (RR)

QoL (misure oggettive)

Eventi avversi (PS o sospensione): **no side effects**

Ricerca entro 9 settembre 2013

RCTs (single or double blinded)
RCTs unblinded

Ogni età ogni epilessia
Ogni tipo di marijuana
(sintetica, naturale, CBD, cannabinolo

26 lavori → **4 STUDI ELIGIBILI (1978-1990)**

Cochrane Library
Cochrane Database of Systematic Reviews
Cochrane Database of Systematic Reviews 2014
DOI: 10.1002/14651858.CD009270.pub3.

Cannabinoids for epilepsy (Review)

Gloss D, Vickrey B

AUTHORS' CONCLUSIONS

Implications for practice

No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy.

There is an insufficient body of evidence to recommend using marijuana to treat epilepsy. The dose of 200 to 300 mg daily of cannabidiol was safely administered to small numbers of patients, for generally short periods of time, and so no conclusions can be drawn about the safety of long term cannabidiol treatment.

Implications for research

There is a body of animal research that suggests that it might be useful to evaluate the efficacy of cannabinoids for treatment of epilepsy in humans. None of the existing clinical research is of sufficient quality or size to answer this question. If the question were to be addressed, there would need to be a series of properly designed, high quality and adequately powered trials.

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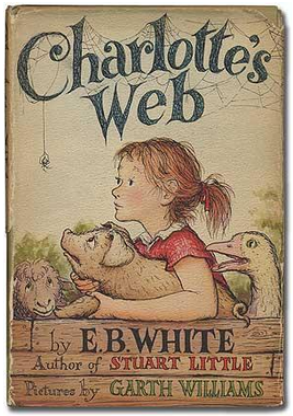

CONTROVERSY IN EPILEPSY

The case for medical marijuana in epilepsy

*†Edward Maa and ‡Paige Figi

Epilepsia, 55(6):783–786, 2014
doi: 10.1111/epi.12610

Charlotte 5 anni: Sindrome di Dravet

Add on: composto con alto CBD:THC (Charlotte's Web)

Drammatica riduzione delle crisi convulsive

Miglioramento complessivo: alimentazione, sonno, relazione

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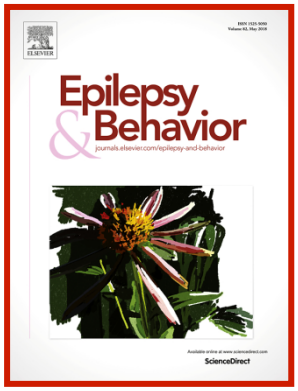
Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

December 2013
Volume 29, Issue 3, p433-602

Brenda E. Porter and
Department of Neurology, Stanford University

Catherine Jacobson
Department of Neurology, Stanford University



Sito facebook: 150 membri
Questionario: 24 domande
Criteri inclusione: 19 risposte
diagnosi di epilessia-uso di cannabis CBD- arricchita

Sito facebook
Dravet-STP

13 DS, 4 MA, 1 LG, 1 «idiopatica»
Età: 2-16 anni

CBD: <0.5- 28.6 mg/Kg/day
THC: 0- 0.8 mg/Kg/day
2 settimane- >12 mesi.

RISCHIO DI BIAS

RIDUZIONE CRISI: 16/19

> 80%:
7/13 DS
3/4 MA
1/1 LG

ALMENO 1 ALTRO EFFETTO POSITIVO: 16/19

ALMENO 1 EFFETTO AVVERSO: 7/19

CONTROVERSY IN EPILEPSY

FONDAZIONE I.R.C.C.S. ISTITUTO NEUROLOGICO CARLO BESTA

The case for assessing cannabidiol in epilepsy

*Maria Roberta Cilio, †Elizabeth A. Thiele, and ‡Orrin Devinsky

Epilepsia, 55(6):787–790, 2014
doi: 10.1111/epi.12635

Dr. Maria Roberta Cilio is a Professor of Neurology and Pediatrics, Director of Pediatric Epilepsy Research, at University of California, San Francisco.

Problematiche legate all'uso «spontaneo»
Composizione dei preparati e loro stabilità nel tempo (possibili variazioni legate a coltivazione ecc)
Selection bias
Effetto placebo
Effetti avversi a breve e lungo termine

CBD promettente ma
Necessario valutare profilo di sicurezza
Dose-tollerabilità
Profilo farmacocinetico
Interazioni
Efficacia potenziale

RCT prospettici
Popolazioni selezionate

JNNP Online First, published on March 6, 2018 as 10.1136/jnnp-2017-317168

FONDAZIONE I.R.C.C.S. ISTITUTO NEUROLOGICO CARLO BESTA

REVIEW

Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence

Emily Stockings,[1] Dino Zagic,[1] Gabrielle Campbell,[1] Megan Weier,[1] Wayne D Hall,[2,3] Suzanne Nielsen,[1] Geoffrey K Herkes,[4] Michael Farrell,[1] Louisa Degenhardt[1]

Box 1

1. Cannabis or marijuana or cannabinoids or endocannabinoids or dronabinol or nabilone or marinol or levonantradol or tetrahydrocannabinol or cesamet or delta-9-THC or delta-9-tetrahydrocannabinol or nabiximols or sativex pr cannabidiol
2. Therapeutic use or drug therapy or analgesics
3. 1 and 2
4. (medical or medicinal) adj (mari?uana or cannab*) or 'medical mari?uana' or 'medicinal cannabis'
5. 3 or 4
6. Epilepsy
7. 5 and 6

1980-0ttobre 2017

30 osservazionali: 2865 pts
CNB vari, > CBD, CBT-THC, cannabis sativa, …

6 RCTs: 555 CBD vs PLA

4 DB CBD vs PLA

1 cross over

(1 vs PLA)

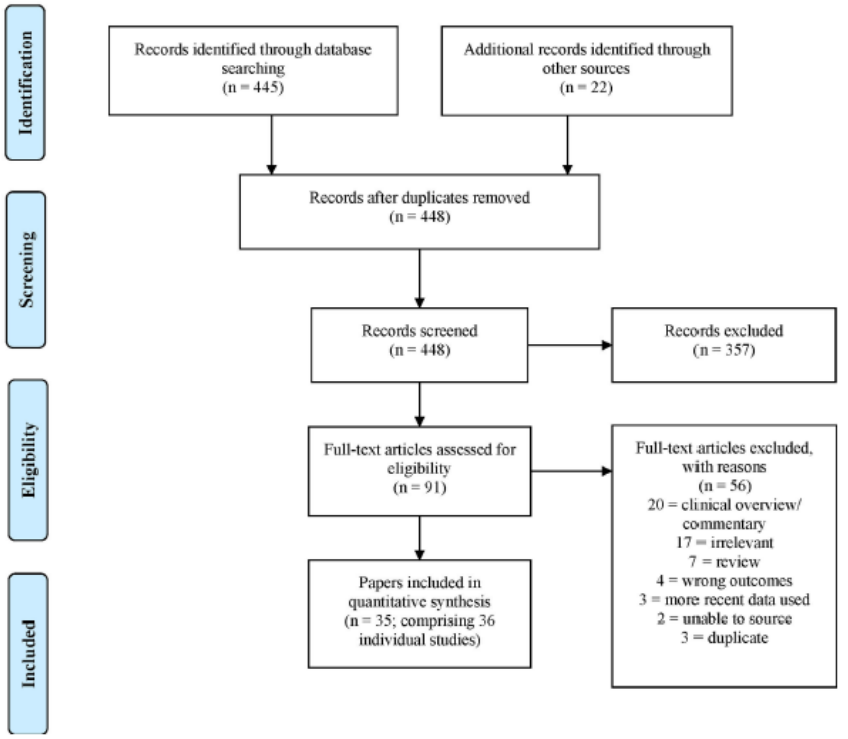


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

JNNP Online First, published on March 6, 2018 as 10.1136/jnnp-2017-317168
Epilepsy

REVIEW

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FONDAZIONE I.R.C.C.S. ISTITUTO NEUROLOGICO CARLO BESTA

OUTCOME PRIMARIO: 50% RIDUZIONE FREQUENZA CRISI
19 studi (2 RCT): Mixed quality evidence that there may be some treatment effect of CBD as adjunctive therapy in achieving 50% or greater reduction in seizures

OUTCOME SECONDARIO: LIBERTA DA CRISI
17 studi (3 RCT): Mixed quality evidence that there may be some treatment effect of CBD as adjunctive therapy may help achieve seizure freedom

OUTCOME SECONDARIO: QUALITA DI VITA
14 studi (2 RCT): Mixed quality evidence that CBD improved patient QoL when used as adjunctive therapy.

OUTCOME SECONDARIO: SOSPENSIONE DEL TRATTAMENTO
12 studi (4RCT): Mixed quality evidence that petients who received CBD were more likely to withdraw from treatment.

JNNP Online First, published on March 6, 2018 as 10.1136/jnnp-2017-317168
Epilepsy

REVIEW

Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence

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FONDAZIONE I.R.C.C.S. ISTITUTO NEUROLOGICO CARLO BESTA

Pochi RCTs di alta qualità
Principalmente epilessie rare pediatriche

Un ragionevole numero di pazienti: riduzione delle crisi

AE minori frequenti
Libertà da crisi improbabile

NECESSARI RCTs

Table 1 Study-level summaries of included randomised controlled trials

Study	Design	Sample	Treatment	Pharma. grade	Outcomes measured	Results	Adverse events and serious adverse events	Bias assessment† /GRADE assessment
Ames and Crindland[30]	Randomised clinical trial	12 adults with frequent seizures not controlled by anticonvulsant therapy (drug-resistant epilepsy)	100 mg CBD or placebo sunflower oil 3 times a day for 1 week, then 2 times a day for 3 weeks	Not stated	Seizure reduction	- The trial was abandoned before the second stage of the trial could take place. No significant differences in seizure frequency were observed between groups.	Reported: drowsiness	Unclear risk/low
Cunha *et al*[15]	Randomised, double-blind, placebo-controlled trial	15 adults (mean age=24; range 14–49; 26.7% male) with secondary generalised epilepsy (drug-resistant epilepsy)	100 mg CBD or placebo glucose capsule, taken orally 2–3 times per day, for 8–18 weeks	Not stated	Reported seizure improvement; self-reported subjective improvement	- Four of seven (~57%) patients receiving CBD showed complete seizure freedom, compared with 1/8 (12.5%) placebo patients. - All 7 CBD patients showed some sort of improvement in seizure frequency, compared with only 2/8 (25%) placebo patients. - One CBD patient withdrew from the study, whereas two patient receiving placebo withdrew.	Somnolence (57.1%) Painful gastric sensation (14.3%)	High risk/moderate
Devinsky *et al*[26]	Randomised, double-blind, placebo-controlled trial	120 children and adolescents (mean age=9.8; range=2–18; 52% male) with Dravet syndrome (drug-resistant epilepsy)	20 mg/kg/day CBD or placebo, taken orally for 14 weeks, as an adjunctive treatment	Yes	Change in seizure frequency, caregiver global impression of change	- Three CBD patients achieved total seizure freedom during the test period, no placebo patients achieved seizure freedom (P=0.08). - Twenty-six CBD patients (~43%) had a >50% reduction in seizures, compared with 16 patients (~27%) in the placebo group. - Thirty-seven caregivers (~62%) judged their child's overall condition to be improved in the cannabidiol group, as compared with 20 (~34%) in the placebo group (P=0.02). - Nine CBD patients withdrew from the study, 8 of which were due to adverse events. In comparison, three placebo patients withdrew, with only one being due to adverse events.	Somnolence (36%) Diarrhoea (31%) Decreased appetite (28%) Fatigue (20%) Vomiting (15%) Fever (15%) Lethargy (13%) Upper respiratory tract infection (11%) Convulsion (11%) *Serious:* Elevated liver aminotransferase enzymes (20%) Status epilepticus (4.9%)	Low risk/high
GW Pharmaceuticals[27]	Randomised, double-blind, placebo-controlled trial	225 patients (mean age=16; range=2–55) with Lennox-Gastaut syndrome (drug-resistant epilepsy)	i) 10 mg/kg/day CBD for 14 weeks	Yes	Change in seizure frequency, change in QoL and caregiver global impression of change	- Patients randomised to 10 mg/kg/day of CBD achieved a median reduction in monthly drop seizures of 37%, in comparison with 17% in those patients in the placebo group (P=0.0016). - One patient receiving 10 mg/kg/day CBD withdrew due to adverse events, as did one placebo patient.	All cause (83.6%) *Serious:* All cause (17.8%)	Unclear risk/high
			ii) 20 mg/kg/day CBD for 14 weeks	Yes	Change in seizure frequency, change in QoL and caregiver global impression of change	- Patients taking 20 mg/kg/day of CBD showed a median reduction in monthly drop seizures of 42%, compared with 17% in the placebo group (P=0.0047). - Six patients receiving the higher dose (20 mg/kg/day) withdrew due to adverse events, compared with one placebo patient.	All cause (93.4%) *Serious:* All cause (17.1%)	
Thiele *et al*[28]	Randomised, double-blind, placebo-controlled study	171 patients (mean age=15.4; range=2–45; 51.5% male) with Lennox-Gastaut syndrome (drug-resistant epilepsy)	20 mg/kg/day CBD or placebo, taken daily for 14 weeks, as an adjunctive treatment	Yes	Change in seizure frequency, caregiver impression of overall improvement	- Five of 86 CBD patients achieved complete seizure freedom during the maintenance period, compared with none in the placebo group. - Thirty-eight patients (~44%) taking CBD had >50% decrease in seizures, compared with 20 (~24%) patients taking placebo. - Forty-two (~58%) CBD patients were reported (by either themselves or a caregiver) to have achieved an improvement in their overall condition, compared with 29 (~34%) placebo patients. - Fourteen CBD patients withdrew from the study, compared with just one patient given placebo.	Diarrhoea (18.6%) Somnolence (15.1%) Fever (12.8%) Decreased appetite (12.8%) Vomiting (10.5%) *Serious:* All cause (23.3%)	Unclear risk/high
Trembly and Sherman[29]	Double-blind, cross-over, placebo-controlled add-on trial	12 adults with incompletely controlled seizures (drug-resistant epilepsy)	100 mg CBD or placebo 3 times per day for 26 weeks	Not stated	Monthly seizure episodes	- Changes to seizure frequency were not statistically analysed, but authors report some reduction in seizure frequency for patients taking CBD.	None reported	Unclear risk/moderate

†Bias assessment based on risk of bias for randomised studies.
Studies are presented in alphabetical order; adverse events are reported for participants receiving cannabinoids and experienced by >10% of sample.
CBD, cannabidiol; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; Pharma. grade, pharmaceutical grade cannabinoid product; QoL, quality of life.

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

Lancet 2018; 391: 1085–96

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

24 centri:USA, Olanda, Polonia

Diagnosi di LG
> 2 drop-attacks/ w nelle 4 settimane precedenti

171 pazienti: età media 15 aa (2-55)

CBD 20 mg/Kg/die vs placebo
(add-on, Clo 50%, VPA, LTG)

2 settimane titolazione (treatment period)
+
12 mantenimento (mantainance)

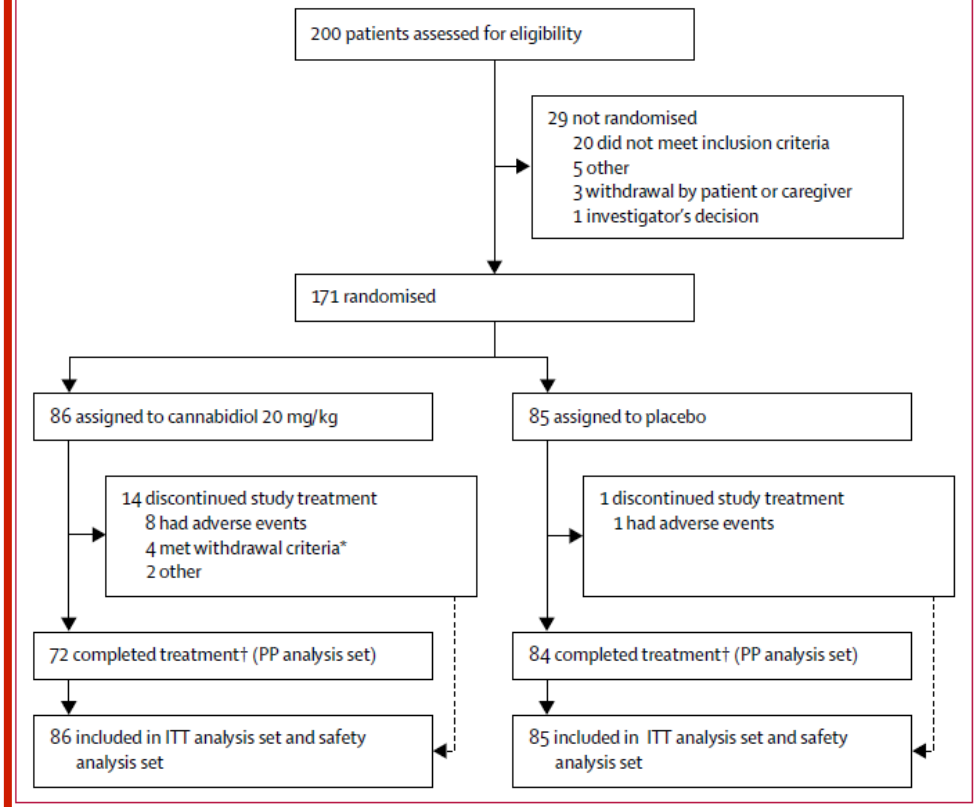

Figure 1: **Trial profile**
PP=per-protocol. ITT=intention-to-treat. *Three of the patients who met withdrawal criteria had elevations in liver transaminases that were considered adverse events. One patient who withdrew for other reasons had a viral infection that was considered an adverse event. †72 patients in the cannabidiol group and 84 in the placebo group were enrolled in the open-label extension trial.

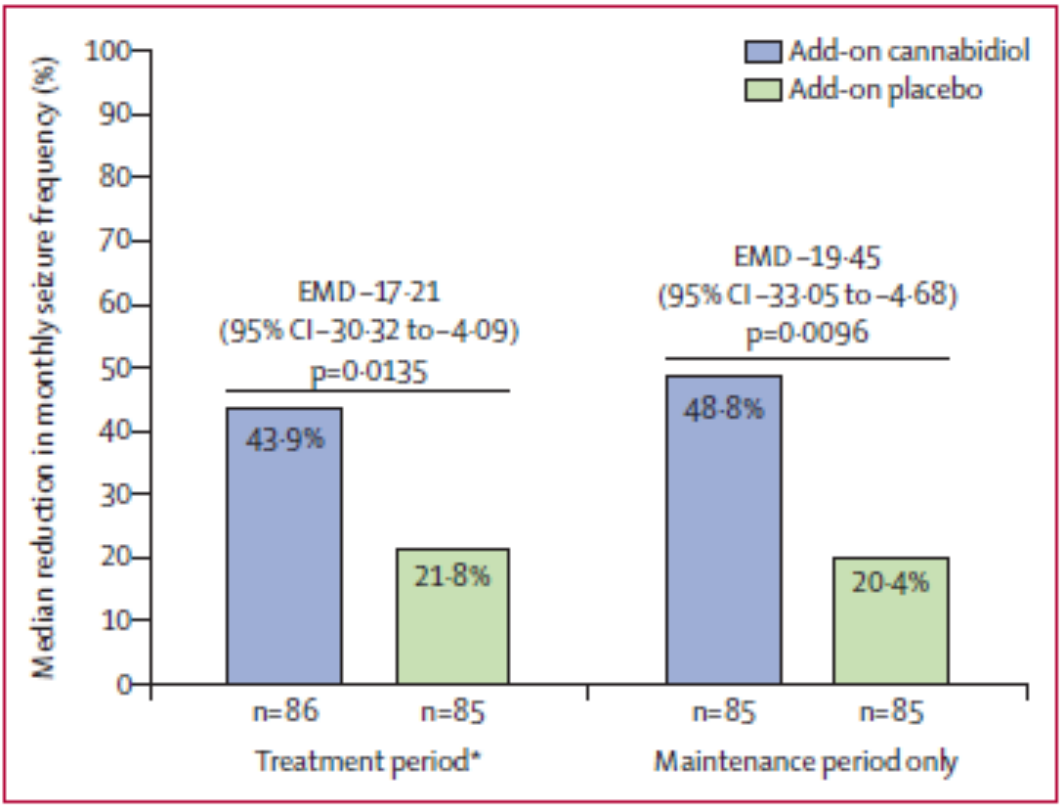

Figure 2: **Reduction in drop seizure frequency during the treatment and maintenance period**

Median percentage reduction in monthly drop seizures during the 14-week treatment period (2 weeks of dose escalation plus 12-week maintenance period alone) in cannabidiol and placebo treatment groups. EMD=estimated median difference. *Primary endpoint.

CBD
20 mg/kg/die

Riduzione mediana DS/mese: 43.9 vs 21.8

Endpoint primario: - 17.2; -19.4
≠ media di frequenza crisi/mese

Endpoint secondario: 44 % vs 24 %
riduzione DS > 50%

Drop Seizure freedom: 3 pazienti vs 0

EFFETTI COLLATERALI:

- 86% CBD vs 69% PLA
- Comuni (= > 10%):

diarrea sonnolenza piressia, ridotto appetito, vomito

- Ritiro dallo studio:

14% in CBD vs 1% in PLA

❖Aumento transaminasi: 20 casi (16 in VPA = 16 su 36 pz in VPA)

❖Regredisce riducendo o togliendo CBD o VPA

❖Polmonite o disturbo del respiro in associazione con Clo (che per effetto CBD su CYP2C19) + sonnolenza = il 27% riduce Clo

	Cannabidiol (n=86)		Placebo (n=85)	
	All cause	Treatment related	All cause	Treatment related
Diarrhoea				
Mild	12 (14%)	9 (10%)	6 (7%)	3 (4%)
Moderate	3 (3%)	2 (2%)	1 (1%)	0
Severe	1 (1%)	0	0	0
All	16 (19%)	11 (13%)	7 (8%)	3 (4%)
Somnolence*				
Mild	5 (6%)	5 (6%)	5 (6%)	4 (5%)
Moderate	8 (9%)	7 (8%)	3 (4%)	3 (4%)
All	13 (15%)	12 (14%)	8 (9%)	7 (8%)
Pyrexia				
Mild	7 (8%)	0	5 (6%)	1 (1%)
Moderate	4 (5%)	1 (1%)	2 (2%)	0
All	11 (13%)	1 (1%)	7 (8%)	1 (1%)
Decreased appetite				
Mild	7 (8%)	5 (6%)	1 (1%)	0
Moderate	3 (3%)	2 (2%)	1 (1%)	1 (1%)
Severe	1 (1%)	1 (1%)	0	0
All	11 (13%)	8 (9%)	2 (2%)	1 (1%)
Vomiting				
Mild	3 (3%)	3 (3%)	9 (11%)	3 (4%)
Moderate	5 (6%)	2 (2%)	5 (6%)	1 (1%)
Severe	1 (1%)	1 (1%)	0	0
All	9 (10%)	6 (7%)	14 (16%)	4 (5%)

Data are n (%). The most common adverse events, defined using Medical Dictionary for Regulatory Activities preferred terms, were events that occurred in more than 10% of patients. Event names were defined according to the Medical Dictionary for Regulatory Activities. *Nine (69%) of 13 patients in the cannabidiol group and seven (88%) of eight patients in the placebo group with somnolence were taking concomitant clobazam.

Table 2: **Most common adverse events**

Limiti dello studio

- Tutti pazienti in politerapia:
- problema interazioni con altri farmaci sia per efficacia che per intolleranza
- In particolare potenziale interazione con VPA e Clb
- Dose fissa
- Scarsa diversità etnica (90% bianchi)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

FONDAZIONE I.R.C.C.S. ISTITUTO NEUROLOGICO CARLO BESTA

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*

225 pazienti

20 mg/KG CBD
10 mg/Kg CBD
placebo

14 settimane trattamento
Riduzione crisi
41.9% vs 37.2% vs 17.2%

Sospensione per eventi avversi
6 vs 1 vs 0

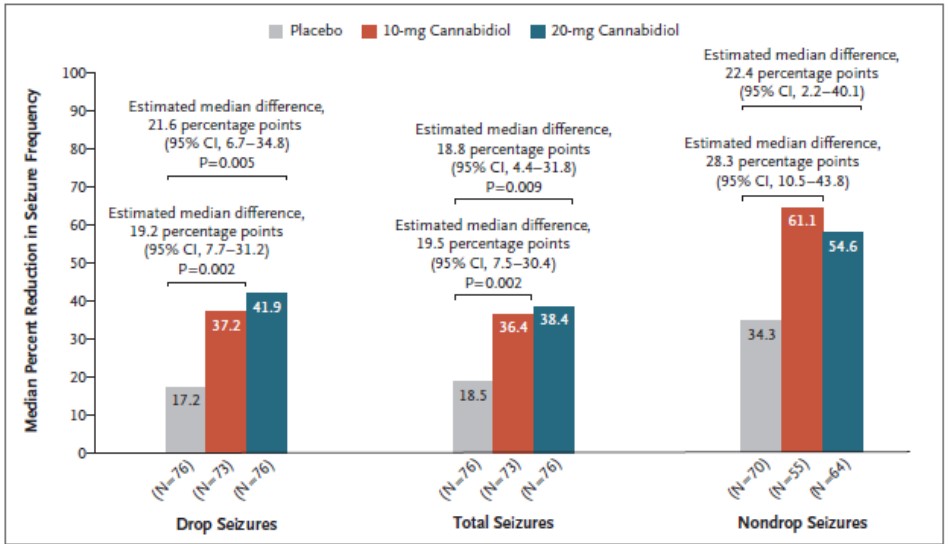

Figure 2. Median Percent Reductions in Monthly Seizure Frequency during the Treatment Period.
The estimated median differences are for the comparisons between each cannabidiol group and the placebo group and were calculated with the use of the Hodges–Lehmann approach. The P values were calculated with the use of a Wilcoxon rank-sum test. Drop seizures are defined as epileptic seizures (atonic, tonic, or tonic–clonic) involving the entire body, trunk, or head that lead or could lead to a fall, injury, or slumping in a chair; total seizures were defined as all types of seizures combined, and nondrop seizures as all seizures except drop seizures. P values for nondrop seizures are not shown because this was not a key secondary outcome, and type 1 error was not controlled.

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

FONDAZIONE I.R.C.C.S. ISTITUTO NEUROLOGICO CARLO BESTA

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*

23 centri:USA, Olanda, Polonia

Diagnosi di Dravet
> 4 crisi convulsive nelle 4 settimane precedenti

120 pazienti: età media 9.8 aa (2-28)

CBD 20 mg/Kg/die vs placebo
(add-on, Clo 65%)

2 settimane titolazione (treatment period)
+
12 mantenimento (mantainance)

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned 120 children and young adults with the Dravet syndrome and drug-resistant seizures to receive either cannabidiol oral solution at a dose of 20 mg per kilogram of body weight per day or placebo, in addition to standard antiepileptic treatment. The primary end point was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period.

Risultati:

frequenza media crisi convulsive/mese
CBD: da 12 a 5.9
PLA: 14.9 a 14.1

50% riduzione crisi convulsive:
43% vs 27%

Seizure freedom: 5% vs 0 (3 pazienti)
Non riduzione significativa delle crisi non convulsive
GIC 62% vs 34%

EFFETTI COLLATERALI nel 75% in CBD vs 37% in PLA.
Nelle prime 2 settimane CBD:
8 pazienti sospendono
12 aumento transaminasi, tutti in VPA: 3 stop
Sonnolenza in 22 CBD: 18 + Clb

Table 2. Adverse events most commonly reported in the randomized double-bind placebo-controlled trial of CBD in comparison with placebo in patients with Dravet syndrome[85]

Adverse event	Percentage of patients with adverse event	
	CBD group (n = 61)	Placebo group (n = 59)
Somnolence	36%	10%
Diarrhea	31%	10%
Decreased appetite	28%	5%
Fatigue	20%	3%
Vomiting	15%	5%
Fever	15%	8%
Lethargy	13%	5%
Convulsion	11%	5%
Upper respiratory tract infection	11%	8%

Only events occurring with a frequency > 10% in either group are listed.
CBD, cannabidiol.

FONDAZIONE I.R.C.C.S.
ISTITUTO NEUROLOGICO CARLO BESTA

CONCLUSIONI

This trial showed that cannabidiol reduced the frequency of convulsive seizures among children and young adults with the Dravet syndrome over a 14-week period but was associated with adverse events including somnolence and elevation of liver-enzyme levels. Additional data are needed to determine the long-term efficacy and safety of cannabidiol for the Dravet syndrome.

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

Correspondence
Dr. Devinsky
Od4@nyu.edu

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

FONDAZIONE I.R.C.C.S. ISTITUTO NEUROLOGICO CARLO BESTA

Abstract

Objective

To evaluate the safety and preliminary pharmacokinetics of a pharmaceutical formulation of purified cannabidiol (CBD) in children with Dravet syndrome.

Methods

Patients aged 4–10 years were randomized 4:1 to CBD (5, 10, or 20 mg/kg/d) or placebo taken twice daily. The double-blind trial comprised 4-week baseline, 3-week treatment (including titration), 10-day taper, and 4-week follow-up periods. Completers could continue in an open-label extension. Multiple pharmacokinetic blood samples were taken on the first day of dosing and at end of treatment for measurement of CBD, its metabolites 6-OH-CBD, 7-OH-CBD, and 7-COOH-CBD, and antiepileptic drugs (AEDs; clobazam and metabolite *N*-desmethylclobazam [N-CLB], valproate, levetiracetam, topiramate, and stiripentol). Safety assessments were clinical laboratory tests, physical examinations, vital signs, ECGs, adverse events (AEs), seizure frequency, and suicidality.

Results

Thirty-four patients were randomized (10, 8, and 9 to the 5, 10, and 20 mg/kg/d CBD groups, and 7 to placebo); 32 (94%) completed treatment. Exposure to CBD and its metabolites was dose-proportional (AUC_{0-t}). CBD did not affect concomitant AED levels, apart from an increase in N-CLB (except in patients taking stiripentol). The most common AEs on CBD were pyrexia, somnolence, decreased appetite, sedation, vomiting, ataxia, and abnormal behavior. Six patients taking CBD and valproate developed elevated transaminases; none met criteria for drug-induced liver injury and all recovered. No other clinically relevant safety signals were observed.

Conclusions

Exposure to CBD and its metabolites increased proportionally with dose. An interaction with N-CLB was observed, likely related to CBD inhibition of cytochrome P450 subtype 2C19. CBD resulted in more AEs than placebo but was generally well-tolerated.

Classification of evidence

This study provides Class I evidence that for children with Dravet syndrome, CBD resulted in more AEs than placebo but was generally well-tolerated.

Interazione con Clobazam (aumento metabolita NCLB)

Effetti avversi piu comuni
febbre sonnolenza
Dimuinuzione appetito vomito atassia comportamento

Significativamente piu che nel gruppo placebo

Ma generalmente ben tollerato

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Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome

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Significance

Medicinal cannabis use is booming despite limited preclinical evidence and mechanistic insight. Recent clinical trials of cannabidiol (CBD) in Dravet syndrome (DS) support its clinical efficacy for reduction of seizure frequency and invite study of its benefits for additional DS symptoms. We demonstrate here that treatment with CBD is beneficial for seizure frequency, duration, and severity and for autistic-like social deficits in a mouse model of DS. CBD rescue of DS symptoms is associated with increased inhibitory neurotransmission, potentially mediated by antagonism of the lipid-activated G protein-coupled receptor GPR55. These studies lend critical support for treatment of seizures in DS with CBD, extend the scope of CBD treatment to autistic-like behaviors, and provide initial mechanistic insights into CBD's therapeutic actions.

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