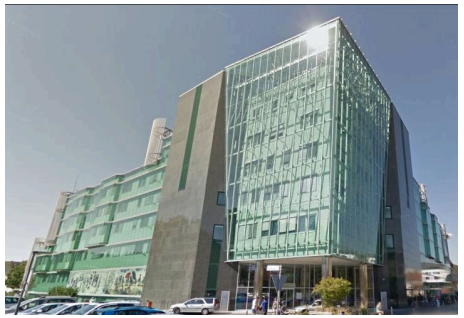
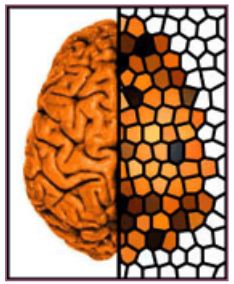
Klinični izsledki zdravljenja s kanabinoidi v otroški nevrologiji

Clinical results of treatment with cannabinoids in Child Neurology





Prof. David Neubauer, MD, PhD
Paediatrician & Child Neurologist
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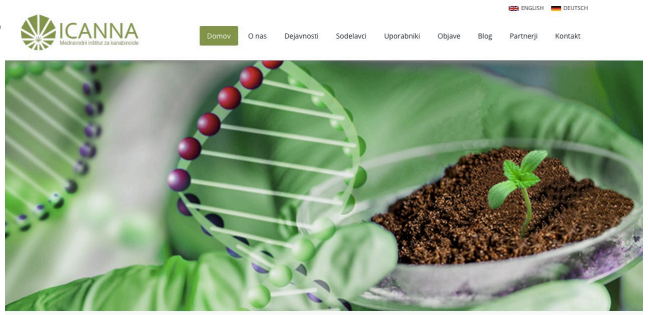
SLOVENIA

Univerza v Ljubljani
Medicinska fakulteta



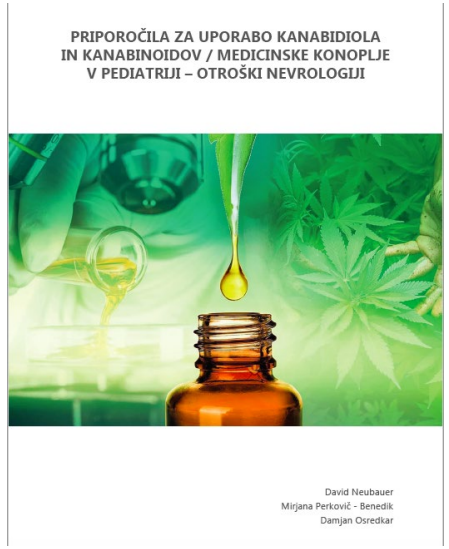
Raziskave medicinske konoplje obetajo nove paradigme zdravljenjea v svetu in pri nas

Ljubljana, Hiša EU, 5. decembar 2022

https://www.institut-icanna.com/en/

Vsebina

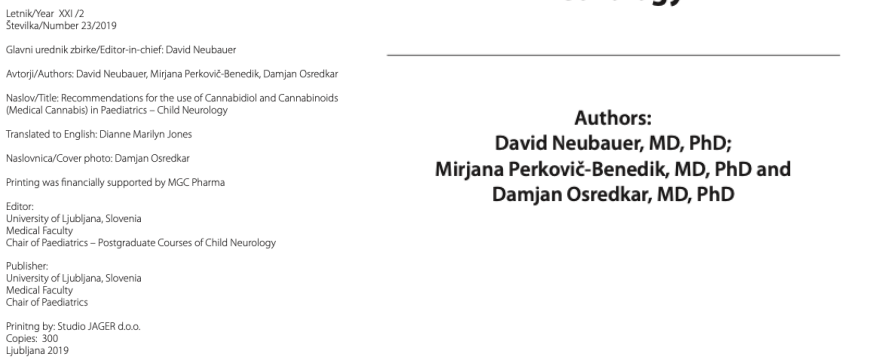
- Možnosti uporabe kananbinoidov v otroški nevrologiji
  - trdovratna epilepsija in sindromi
  - nevrorazvojne motnje in sindromi
  - avtizem in podobne motnje vedenja
  - spastičnost in cerebralna paraliza



Contents

Potential therapeutic use of cannabinoids in Child Neurology:

- resistant epilepsies and syndromes
- neurodevelopmental disorders and syndromes
- autism and related disorders of behavior
- spasticity & cerebral palsy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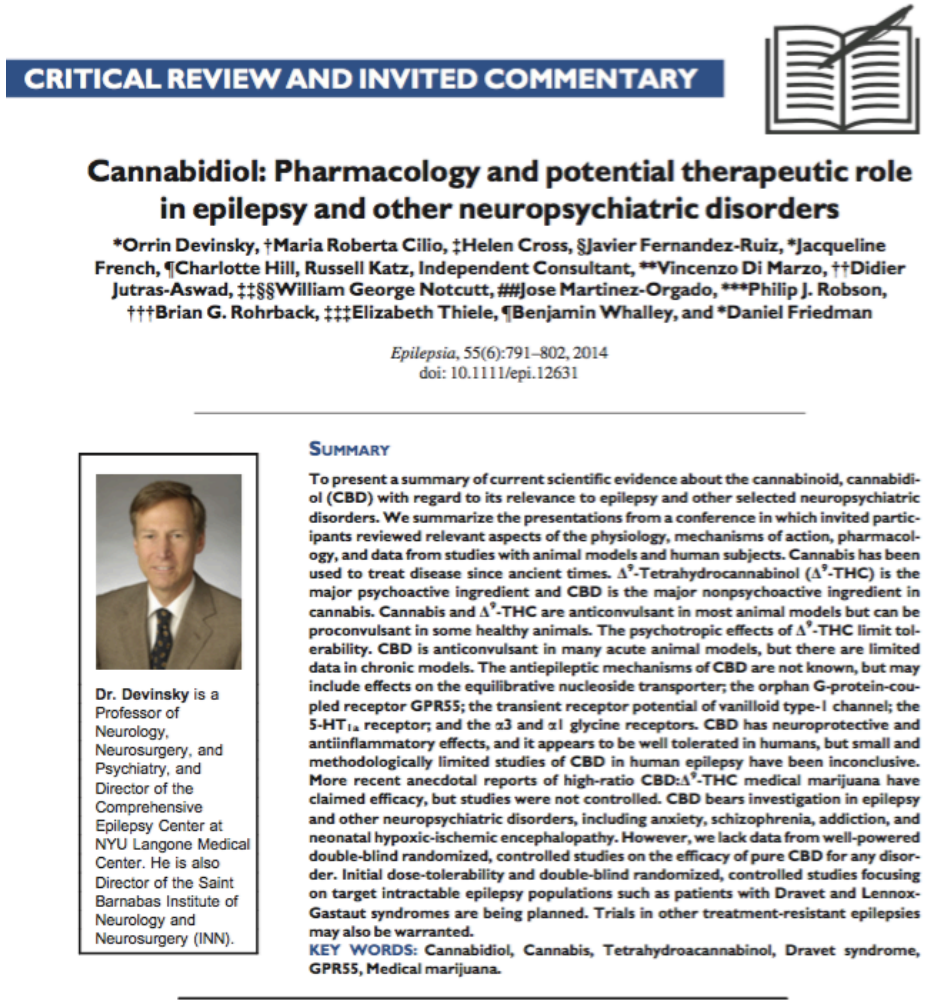
Recommendations for the use of cannabidiol and cannabinoids (medical cannabis) in paediatrics – child neurology

Authors:
David Neubauer, MD, PhD;
Mirjana Perkovič-Benedik, MD, PhD and
Damjan Osredkar, MD, PhD

Možnosti uporabe kanabinoidov v otroški nevrologiji

Current scientific evidence for efficacy:

- painful HIV-associated sensory neuropathy
- chronic pain
- **C**hemotherapy-induced nausea & vomiting
- **A**ddiction
  Neonatal hypoxic-ischaemic encephalopathy
  Neuropathic pain
- **A**nxiety
- **B**ehavioral problems, neurodevelopmental sy.
- **I**ntellectual disability/autism
- **S**eizures & Epilepsy (DEE, different syndromes)
- spasms in patients with cerebral palsy



CRITICAL REVIEW AND INVITED COMMENTARY

Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders

*Orrin Devinsky, †Maria Roberta Cilio, ‡Helen Cross, §Javier Fernandez-Ruiz, *Jacqueline French, ¶Charlotte Hill, Russell Katz, Independent Consultant, **Vincenzo Di Marzo, ††Didier Jutras-Aswad, ‡‡§§William George Notcutt, ##Jose Martinez-Orgado, ***Philip J. Robson, †††Brian G. Rohrback, ‡‡‡Elizabeth Thiele, ¶Benjamin Whalley, and *Daniel Friedman

Epilepsia, 55(6):791–802, 2014
doi: 10.1111/epi.12631

Dr. Devinsky is a Professor of Neurology, Neurosurgery, and Psychiatry, and Director of the Comprehensive Epilepsy Center at NYU Langone Medical Center. He is also Director of the Saint Barnabas Institute of Neurology and Neurosurgery (INN).

Summary

To present a summary of current scientific evidence about the cannabinoid, cannabidiol (CBD) with regard to its relevance to epilepsy and other selected neuropsychiatric disorders. We summarize the presentations from a conference in which invited participants reviewed relevant aspects of the physiology, mechanisms of action, pharmacology, and data from studies with animal models and human subjects. Cannabis has been used to treat disease since ancient times. Δ^9-Tetrahydrocannabinol (Δ^9-THC) is the major psychoactive ingredient and CBD is the major nonpsychoactive ingredient in cannabis. Cannabis and Δ^9-THC are anticonvulsant in most animal models but can be proconvulsant in some healthy animals. The psychotropic effects of Δ^9-THC limit tolerability. CBD is anticonvulsant in many acute animal models, but there are limited data in chronic models. The antiepileptic mechanisms of CBD are not known, but may include effects on the equilibrative nucleoside transporter; the orphan G-protein-coupled receptor GPR55; the transient receptor potential of vanilloid type-1 channel; the 5-HT_{1A} receptor; and the α3 and α1 glycine receptors. CBD has neuroprotective and antiinflammatory effects, and it appears to be well tolerated in humans, but small and methodologically limited studies of CBD in human epilepsy have been inconclusive. More recent anecdotal reports of high-ratio CBD:Δ^9-THC medical marijuana have claimed efficacy, but studies were not controlled. CBD bears investigation in epilepsy and other neuropsychiatric disorders, including anxiety, schizophrenia, addiction, and neonatal hypoxic-ischemic encephalopathy. However, we lack data from well-powered double-blind randomized, controlled studies on the efficacy of pure CBD for any disorder. Initial dose-tolerability and double-blind randomized, controlled studies focusing on target intractable epilepsy populations such as patients with Dravet and Lennox-Gastaut syndromes are being planned. Trials in other treatment-resistant epilepsies may also be warranted.

KEY WORDS: Cannabidiol, Cannabis, Tetrahydroacannabinol, Dravet syndrome, GPR55, Medical marijuana.

vse možne indikacije v otroški nevrologij

It all started with the story of small girl Charlotte who had Dravet syndrome and > 200 seizures daily

> 2014

Published in final edited form as:
Epilepsia. 2014 June ; 55(6): 791–802. doi:10.1111/epi.12631.

Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders

Orrin Devinsky[1], **Maria Roberta Cilio**[2], **Helen Cross**[3], **Javier Fernandez-Ruiz**[4], **Jacqueline French**[1], **Charlotte Hill**[13], **Russell Katz**[5], **Vincenzo Di Marzo**[6], **Didier Jutras-Aswad**[7], **William George Notcutt**[8], **Jose Martinez-Orgado**[9], **Philip J. Robson**[10], **Brian G. Rohrback**[11], **Elizabeth Thiele**[12], **Benjamin Whalley**[13], and **Daniel Friedman**[1]

Cannabis plants grown in Colorado were used to treat Charlotte's epilepsy, but researchers are heading to Israel to study the drug.

ISRAEL

Research without prejudice

How one Mediterranean country is pushing the frontiers of medical cannabis knowledge.

BY EMILY SOHN

Alan Shackelford is intent on finding out why some of his patients respond so well to cannabis. But despite living in Colorado, the US state with some of the most liberal medical marijuana laws, he has had to travel to Israel to continue his research.

Shackelford's road to the Mediterranean nation started in 2012. While working in occupational medicine and injury rehabilitation private practice, he got a call from a mother whose 5-year-old daughter Charlotte was having 300 seizures a week and not responding to treatment. The family were desperate for help. They had heard that medical marijuana was being used to treat epilepsy, but had been turned away by doctors when they asked for the treatment for Charlotte. Although Shackelford had finally agreed to treat his older patients with cannabis a few years earlier, he was particularly reluctant to give the herb to such a young child. But, after digging into the literature, Shackelford agreed to treat Charlotte with a specific strain high in cannabidiol (CBD), which a friend of the family converted into an oil extract.

Now 8, Charlotte is thriving. She takes the oil every day and has just one seizure every month or so, Shackelford reports. He has seen other, similar stories, but such case reports and testimonials do not constitute peer-reviewed evidence. However, when he looked into getting permission for a trial, he was overwhelmed by the bureaucracy involved. At a federal level, cannabis is classified as a schedule 1 drug, meaning that it has no known medical value. Unless the study looks at the harm the drug might cause, permission for cannabis research can be harder to obtain than that for heroin or cocaine, says Shackelford. "There is a bias against doing trials here that might show a benefit."

Frustrated, he went to Israel — one of only a few countries with a national medical cannabis research programme. Shackelford was attracted by the country's 50-year history of study into potential uses for the drug, as well as a supportive regulatory atmosphere that is not found anywhere else. "The attitude towards research in Israel has always been different and not coloured by prejudice or propaganda," Shackelford says. Reputable researchers who want to study cannabis are not simply dismissed, he says, "which is often the case in other countries, including, notoriously, the US".

Other researchers and entrepreneurs are, like Shackelford, turning to Israel to further research into cannabis. "It's a topic in which, maybe surprisingly, Israel is pushing ahead," says Raphael Mechoulam, a chemist at The Hebrew University of Jerusalem.

NATURE.COM
Read more about the research challenges at: go.nature.com/tg6d9v

GOOD PARENTING

The modern era of cannabis research started in Israel, spearheaded by Mechoulam (see page S10) — often called the father of medical cannabis. In fact, Shackelford's decision to treat Charlotte was influenced by Mechoulam's research into CBD (J. M. Cunha *et al Pharmacology* **21**, 175–185; 1980).

Today, Israel is one of many places that boasts a broad supportive atmosphere for cannabis: some 75% of the population back its medicinal use, and in 2013 the Orthodox rabbi Efraim Zalmanovich ruled that medical cannabis was kosher.

Israel also seems to nurture an entrepreneurial spirit, which is apparent in Mechoulam's story. Originally from Bulgaria, Mechoulam began investigating cannabis in the 1960s while working at the Weizmann Institute of Science in Rehovot. He was attracted by the mystery: although the active constituents of coca leaves and opium were known, cannabis was still largely unstudied.

Before he could start his research, Mechoulam needed to procure some cannabis

Epilepsia
Official Journal of the International League Against Epilepsy

Controversy in Epilepsy

The case for assessing cannabidiol in epilepsy

Maria Roberta Cilio, Elizabeth A. Thiele, Orrin Devinsky

First published: 22 May 2014 | https://doi.org/10.1111/epi.12635 | Citations: 39

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

Orrin Devinsky, Eric Marsh*, Daniel Friedman*, Elizabeth Thiele, Linda Laux, Joseph Sullivan, Ian Miller, Robert Flamini, Angus Wilfong, Francis Filloux, Matthew Wong, Nicole Tilton, Patricia Bruno, Judith Bluvstein, Julie Hedlund, Rebecca Kamens, Jane Maclean, Srishti Nangia, Nilika Shah Singhal, Carey A Wilson, Anup Patel, Maria Roberta Cilio*

Lancet Neurol 2016; 15: 270–78

Summary

Background Almost a third of patients with epilepsy have a treatment-resistant form, which is associated with severe

Epidiolex (Cannabidiol): A New Hope for Patients With Dravet or Lennox-Gastaut Syndromes

Jeffrey W. Chen, MBA, Laura M. Borgelt, PharmD, FCCP, BCPS, Allison B. Blackmer, PharmD, BCPS, BCPPS, FCCP

First Published January 8, 2019 | Review Article | Check for updates
https://doi.org/10.1177/1060028018822124

Epilepsia
Official Journal of the International League Against Epilepsy

FULL-LENGTH ORIGINAL RESEARCH | Open Access

Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study

Elizabeth Thiele, Eric Marsh, Maria Mazurkiewicz-Beldzinska, Jonathan J. Halford, Boudewijn Gunning, Orrin Devinsky, Daniel Checketts, Claire Roberts

First published: 11 February 2019 | https://doi.org/10.1111/epi.14670 | Citations: 14

Resistant epilepsies* and epileptic syndromes*

- Purifed extract – cannabidiol has been approved by FDA (Epidiolex®) and EMA (Epidyolex®) for certain epileptic syndromes (e.g. Dravet, Lennox-Gastaut, TS complex)
- It has been proven that it is very effective in other resistant epilepsies and so- called developmental epileptic encephalopathies (DEE)
- Also natural, full-spectrum cannabis extracts and "artisanal preparations" have proven efficacy in these cases,
- …and sometimes even superiority

Porcari GS, Fu C, Doll ED, Carter EG, Carson RP. Efficacy of artisanal preparations of cannabidiol for the treatment of epilepsy: Practical experiences in a tertiary medical center. *Epilepsy and Behavior*. 2018;80:240-246.

Sulak D, Saneto R, Goldstein B. The current status of artisanal cannabis for the treatment of epilepsy in the United States. *Epilepsy and Behavior*. 2017;70:328-333.

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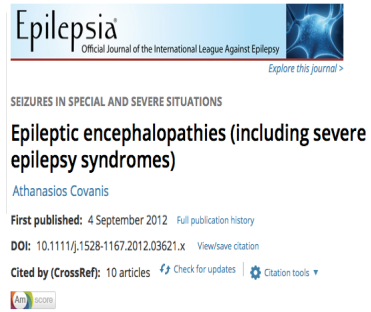
*Devinsky O, Verducci C, Thiele EA, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. *Epilepsy and Behavior*. 2018;86:131-137

*Thiele E, Marsh E, Mazurkiewicz-Beldzinska M, et al. Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. *Epilepsia*. 2019;60(3):419-428.

*Lattanzi S, Trinka E, Striano P, Rocchi C, Salvemini S, Silvestrini M, Brigo F. Highly Purified Cannabidiol for Epilepsy Treatment: A Systematic Review of Epileptic Conditions Beyond Dravet Syndrome and Lennox–Gastaut Syndrome. CNS Drugs. 2021; 35:265–281

Burden of childhood resistant epilepsies/ encephalopathies – today so-called DEE – Developmental Epileptic Encepahlopathies



- Poor Quality of Life (QoL)
- Decline of cognitive and/or motor abilities
- Severe psychosocial problems
- Restricted life-style
- Frequent injuries
- Increased mortality
- Frequently genetic
- Many side effects of treatment

How we started

A. Pacient, ki še ne prejema CBD

1. Glede na odsotnost prepričljivih znanstvenih dokazov za učinkovitost CBD za zdravljenje trdovratnih epilepsij, se CBD aktivno ne promovira / uporablja za zdravljenje trdovratnih epilepsij
2. Če starši vprašajo za alternativne možnosti zdravljenja trdovratnih epilepsij ali konkretno vprašajo po zdravljenju s CBD, se jim razloži možnost zdravljenja s CBD z lekarniškim preparatom (sintetičnim CBD), pojasniti pa je potrebno tako potencialne prednosti, kot slabosti.

B. Pacient že jemlje biološki preparat, ki vsebuje CBD + THC (bCBD; doma pripravljen izdelek z znano ali pa neznano koncentracijo CBD/THC)

1. Pacientu, ki jemlje bCBD, se svetuje, da preide na v lekarni UKCL pripravljen preparat s sintetičnim CBD, po shemi, ki jo je pripravila Mirjana, po orignalni shemi Devinsky et al. (v naprej shema)
2. Pacient, ki jemlje bCBD, in bi rad na njem ostal, se odmerke prilagodi po shemi
3. Pacientu, ki jemlje bCBD in bi želel na lekarniški preparat, ki vsebuje tudi THC, se lahko po naročilu s pomočjo Lee Pečjak v lekarni UKCL izdela sintetičen pripravek, ki vsebuje CBD:THC v razmerju 20:1; prilagoditev odmerka po shemi
4. Pacientu, ki je jemal lekarniški ali farmacevtski CBD in bi rad nazaj na bCBD, se to odsvetuje, če pa pacient vztraja, se odmerke prilagodi prilagodi po shemi

January 2015

We do not promote CBD treatment by ourselves but we wait until the parents ask also for this possibility, and offer them isolated (pure) CBD on prescription.
If there is no effect, than we instruct them how to use preparations as HH or CW, first with high content of CBD

.. If not successful than cannabis with high ratio CBD/THC (from 30/1 do 25/1 to 20/1)
Haleigh's Hope
or
Charlotte Web

PROTOCOL FOR THERAPY WITH CANNABIDIOL: DOSAGE, SAFETY MEASURES

DOSAGE

Starting dose: 2mg/kg BW/day, BID;
The dose will be increased gradually every week by 2mg/kg BW/day; BID, if tolerated
Increasing dose up to **16 mg/kg/day**

Indications: Epileptic encephalopathy, intractable childhood epilepsy (including Dravet syndrome, Lennox-Gastaut Syndrome

PROTOCOL

At 0 week:
-evaluation of the seizure dairy, clinical and neurological evaluation,
-complete blood count, liver function tests, BUN, creatinine will be drawn for baseline, concomitant AED levels
- baseline EEG
- Starting dose: 2 mg/kg BW/day; 2 equally divided doses added to current antiepileptic drug regimen

At week 2:
-patient will return for clinical/neurological evaluation, further increasing of the dose (increase in medication as tolerated by 2 mg/kg BW/day every week)
-evaluation of seizure diary

At week 4:
-patient will return for clinical/neurological evaluation , further increasing of the dose (increase in medication as tolerated by 2 mg/kg BW/day every week)
-evaluation of seizure diary
-control of complete blood count, liver function tests, BUN, creatinine, concomitant AED levels
-control EEG

At week 8/12:
-patient will return for clinical/neurological evaluation, further increasing of the dose up to 16 mg/kg/day, if tolerated
-evaluation of seizure diary
-control of complete blood count, liver function tests, BUN, creatinine, concomitant AED levels,
- control EEG

Ethical approval already in 2013

KOMISIJA REPUBLIKE SLOVENIJE ZA MEDICINSKO ETIKO

Dr. Mirjana Perkovič Benedik, dr. med.
KO za otroško, mladostniško in razvojno nevrologijo
Pediatrična klinika, Univerzitetni klinični center Ljubljana
Bohoričeva 20, 1525 Ljubljana

Štev.: 103/10/13
Datum: 18. 11. 2013

Spoštovana gospa dr. Perkovič Benedik,

Komisiji za medicinsko etiko (KME) ste 24. 10. 2013 poslali v oceno predlog raziskave z naslovom:

"Terapija z medicinskim kanabisom (kanabidiolom, brez psihoaktivnega THC) pri farmakorezistentnih epilepsijah pri otrocih."

KME je na seji 29. oktobra 2013 ocenila, da je raziskava etično sprejemljiva, in Vam s tem izdaja svoje soglasje. Prosimo pa Vas za sprotno poročanje o rezultatih in neželenih pojavih.

Lep pozdrav,

prof. dr. Jože Trontelj
predsednik Komisije RS za medicinsko etiko

Our study

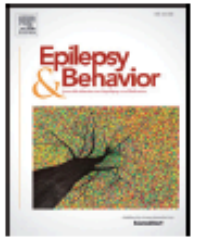
March 2018

Epilepsy & Behavior 81 (2018) 79–85

Contents lists available at ScienceDirect

Epilepsy & Behavior

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



Cannabidiol for treatment of refractory childhood epilepsies: Experience from a single tertiary epilepsy center in Slovenia

David Neubauer, Mirjana Perković Benedik, Damjan Osredkar *

Department of Child, Adolescent and Developmental Neurology, University Children's Hospital, University Medical Centre Ljubljana, Slovenia

Outcome

Epilepsy & Behavior 81 (2018) 79–85

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Department of Child, Adolescent and Developmental Neurology, University Children's Hospital, University Medical Centre Ljubljana, Slovenia

Table 1
Outcome regarding the percentage of seizures in a cohort of 66 patients treated with CBD.

Outcome	No. of patients (%)
Seizure-free	14 (21.2%)
>90% improvement	7 (10.6%)
75%–90% improvement	8 (12.1%)
50%–75% improvement	3 (4.5%)
25%–50% improvement	9 (13.6%)
<25% improvement	10 (15.2%)
No improvement	15 (22.7%)
Worsening of seizures	None

> 50% reduction in 48,5 % children

Died 2 (3%)

1 child with severe ID and multiple brain cavernomas (sudden death during sleep)

1 child with SPTAN mutation – severe ID, severe epilepsy, DQ < 20 due to BPN

ID = intellectual disability, DQ = developmental quotient, BPN = bronchopneumonia

Our study – side effects

- 1x adynamic, floppy, not able to walk but dose 20mg/kg/d;
- 1 x ⬆eosinophils – 8%
- 1 x yellowish skin discoloration
- 1 x enuresis and looks sedated (at a dose of 1000 mg/d)
- 1 x ⬆AST and ALT + pain in stomach

Our study - other (beneficial) effects

Better gross motor functions: 5 x
Better cognitive functions: 3 x
Better behavior: 4 x
Better appetite: 3 x
Better sleep: 3 x
More joyfull: 2 x
More fresh and more alert: 2 x
Better eye-to-eye contact: 1 x
Better communication: 2 x
Shorter duration of seizures: 1 x
Better non-verbal communication and contact: 1 x
Less severe seizures: 1 x
Better speech: 1 x

Drugs of Today 2019, 55(3): 177-196
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CCC: 1699-3993/2019
DOI: 10.1358/dot.2019.55.3.2909248

Clarivate Analytics

Monograph

Cannabidiol as adjunctive treatment of seizures associated with Lennox–Gastaut syndrome and Dravet syndrome

S. Lattanzi[1], E. Trinka[2-4], E. Russo[5], P. Striano[6], R. Citraro[5], M. Silvestrini[1] and F. Brigo[7,8]

[1]Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy; [2]Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University, Salzburg, Austria; [3]Center for Cognitive Neuroscience, Salzburg, Austria; [4]Public Health, Health Services Research and HTA, University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria; [5]Department of Science of Health, University of Catanzaro, Catanzaro, Italy; [6]Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, "G. Gaslini" Institute, University of Genoa, Genova, Italy; [7]Department of Neuroscience, Biomedicine and Movement Science, University of Verona, Verona, Italy; [8]Division of Neurology, "Franz Tappeiner" Hospital, Merano, Bolzano, Italy

21.2% seizure-free
48,5 % > 50%

3% seizure-free
33% > 50%

10% seizure-free
45% > 50%

14.9% seizure-free
44% > 50%

24% seizure-free
49% improvement

88% some improvement
52% > 50%

Summary of the retrospective studies –
SIMILAR STUDIES > SIMILAR RESULTS

Reference	Study population	Treatment	Main findings
Sulak et al. 2017 (71)	272 patients with TRE *Washington cohort* 47 patients (DS: n = 6). Age range: 2-18 years. Male: 43%. Average number of concomitant AEDs: 2.5 *California cohort* 225 patients (LGS: n = 15; DS: n = 12). Age range: 2-46 years. Average number of concomitant AEDs: 3	Artisanal or hemp-based CBD and/or other related products (CBD, THC, THCA)	Of 272 combined patients from both cohorts, 37 (14%) experienced no effect of cannabis at reducing seizures, 29 (15%) had a 1-25% reduction in seizures, 60 (18%) had a 26-50% reduction in seizures, 45 (17%) had a 51-75% reduction in seizures, 75 (28%) had a 76-99% reduction in seizures and 26 (10%) showed a complete clinical response Overall, AEs were mild and infrequent; the most common were somnolence, decreased appetite and fatigue (Washington cohort). Beneficial side effects such as increased alertness were reported DS (Washington cohort). Out of 6 patients, 2 stopped taking CBD due to ineffectiveness, and 4 had seizure frequency reduction
Treat et al. 2017 (72)	119 patients with TRE (LGS: n = 19; DS: n = 17)**** Mean age: 7.5 (range 0.6-18) years	Mixed oral cannabis extracts Mean treatment duration: 11.7 (range 0.3-57) months	Parents of 58 (49%) patients reported at least some improvement in seizures, and 24% of the patients were considered as responders. AEs were reported in 19% of the patients, with the most common being worsening of seizures, somnolence and gastrointestinal symptoms. There were 84 drug withdrawals (71%), 13 of which were due to AEs LGS. 11/19 (58%) patients achieved a seizure frequency reduction ≥ 50%; LGS was the only syndrome type found to be associated with a significantly higher proportion of responders, in comparison to the entire cohort ($P < 0.05$) DS. 1/17 (6%) patient achieved a seizure frequency reduction ≥ 50%; DS significantly impacted duration of treatment, being associated with shorter drug use
Tzadok et al. 2016 (73)	74 patients with TRE Age range: 1-18 years	CBD-enriched cannabis oil with 20:1 CBD:THC ratio, up to 20 mg/kg/day of CBD CBD < 10 mg/kg/day: n = 60 (81%); CBD > 10 mg/kg/day: n = 14 (19%) Median treatment duration: 5.5 (range 3-12) months	66 (89%) patients achieved a reduction in seizure frequency; 13 (18%) had a 75-100% reduction, 25 (34%) had a 50-75% reduction, 9 (12%) had a 25-50% reduction and 19 (26%) had a < 25% reduction 5 (7%) patients reported aggravation of seizures leading to CBD withdrawal Improvements were noted in behavior and alertness, language, communication, motor skills and sleep A total of 5 (6.8%) patients withdrew CBD due to AEs. AEs were reported by 34/74 patients; somnolence/fatigue (n = 16), seizure aggravation (n = 13) and gastrointestinal disturbances/irritability (n = 5) were the most common
Neubauer et al. 2018 (68)	70 patients with TRE (LGS: n = 2). Median age: 8.0 (range 0.5-23.0) years Male: 57%	Crystalline CBD power (> 98% pure) mixed into oil solution (100 mg CBD/mL), up to 16 mg/kg/day	32 (48.5%) out of 66 patients had a ≥ 50% improvement in baseline seizure frequency, 14 of whom (21.2%) became seizure-free. None of the patients reported worsening of seizure frequency, but CBD had no effect in 15 (22.7%) patients. Shorter duration of seizures or shorter time to recovery was observed in some cases
Press et al. 2015 (69)	75 patients with TRE (LGS: n = 9; DS: n = 13) Mean age: 7.3 (range 0.5-18.3) years Male: 45%	Oral cannabis extracts (CBD-only: n = 52; CBD + other oral cannabinoid extract: n = 8; THCA-only: n = 5; other: n = 10) Mean treatment duration: 5.6 (range 1-24) months	Parents of 43 (57%) patients reported at least some improvement; 25 (33%) patients were reported to have > 50% reduction in seizures and 2 (3%) patients were seizure-free at their last follow-up Of the 30 patients with EEG data prior to and during treatment, 3 (10%) had an improvement in interictal background (decrease in spike-wave discharges, improvement in background slowing). None of the 8 responders with EEG data had any interictal improvement. Improvements in behavior/alertness (33%), language (10%) and motor skills (10%) were also reported Treatment was discontinued in 11 (15%) cases. AEs occurred in 44% of patients; the most frequent were seizure worsening (13%), somnolence/fatigue (12%) and gastrointestinal symptoms (11%) LGS and DS. 8/9 (89%) and 3/13 (23%) patients with LGS and DS achieved > 50% reduction in seizures, respectively
Porcari et al. 2018 (70)	176 patients with TRE (LGS: n = 79; DS: n = 8) - CBD group (n = 48; LGS: n = 12; mean age: 10.4 (range 1.1-18) years, male: 52% - CBD + CLB group (n = 54; LGS: n = 27; DS: n = 4); mean age: 7.8 (range 1.4-16) years, male: 56% - CLB group (n = 74; LGS: n = 40; DS: n = 4); mean age: 8.5 (range 1.4-18) years, male: 54%	Artisanal CBD preparations with varying concentrations Average CBD dose: 2.9 mg/kg/day in CBD group, 5.8 mg/kg/day in CBD + CLB group Average treatment duration: 1.1 years in CBD, 1.3 years in CBD + CLB and 2.5 years in CLB groups	No seizures were reported at follow-up in 14%, 9% and 11% of patients in the CBD, CBD + CLB and CLB groups, respectively. After addition of CBD or CLB, 33%, 44% and 38% of patients in the CBD, CBD + CLB and CLB groups had a > 50% reduction in seizure frequency The most common AE in the CBD group was sedation, observed in > 4% of patients (all taking concomitant CLB). Increased alertness and improved verbal interactions were reported in 14% of patients on CBD and 8% of patients on CBD + CLB. The response to CBD was suggested to be independent of concurrent CLB use, although CLB contributed to sedation LGS. Reduction in baseline seizure frequency ≥ 50% was achieved by 58% of children who received CBD alone, 52% of those who received CBD + CLB and 40% in the CLB group

seizure free: from 3 % to 24%
> 50% reduction: from 33% to 52%

S. Lattanzi et al.
Drugs of Today 2019, 55(3): 177-196

In 2015 small group of children treated by artisanal cannabis

10 patients: 7 from Slovenia*
and 3 from Macedonia

"domestic products"

Age: 2 – 24 y

Sex: 4 M, 6 F

1 no effect
6 no seizures
(**60%?**)
2 reduction:
25%-50%
1 < 25%

*THC: 2,5 mg/g (0,25%)
CBD: 34 mg/g (3,4 %)
CBN 0,6 mg/g (0,06%)

approx. 14:1

Dose: 3-5 mg/kg/d

RADIŠIČ, Božidar, HORNBY, Paul, NEUBAUER, David. Clinical observations of 15 cases of encephalopathy/epilepsy/cerebral palsy using standardized natural product cannabis. V: *Cannabinoid conference 2015 : program and abstracts*. p. 113.

outcome

Artisanal cannabis products for treatment of refractory childhood epilepsies

Neubauer David, MD, PhD[1,3]; Žigon Dušan, PhD[2]; Perković Benedik Mirjana, MD, PhD[1,3]; Neli Bizjak, MD, PhD[1,3]; Osredkar Damjan, MD, PhD[1,3]

[1] University Medical Centre Ljubljana, University Children's Hospital, Department of Child, Adolescent and Developmental Neurology, Slovenia

[2] Jožef Stefan Institute, Department of Environmental Sciences, Ljubljana, Slovenia

[3] University of Ljubljana, Faculty of Medicine, Center for Developmental Neuroscience, Slovenia

Sent for publication >

- In summary, our small study suggests that CBD-rich whole plant cannabis extracts are safe to use, with potentially better efficacy than CBD alone, most probably due to the synergistic effect of THC and other cannabinoids.
- The ratio of CBD:THC in the examined preparations was from

  3:1 to 70:1, and all preparations contained other phytocannabinoids as well.
- We were unable to expose any significant differences between different artisanal products regarding effect on seizures and/or quality of life, mainly due to small sample size
- Larger, prospective and controlled studies are needed for stronger evidence on whether whole plant cannabis extracts are more effective than CBD alone for treatment of children with refractory epilepsy.

Other possible effects of cannabinoids

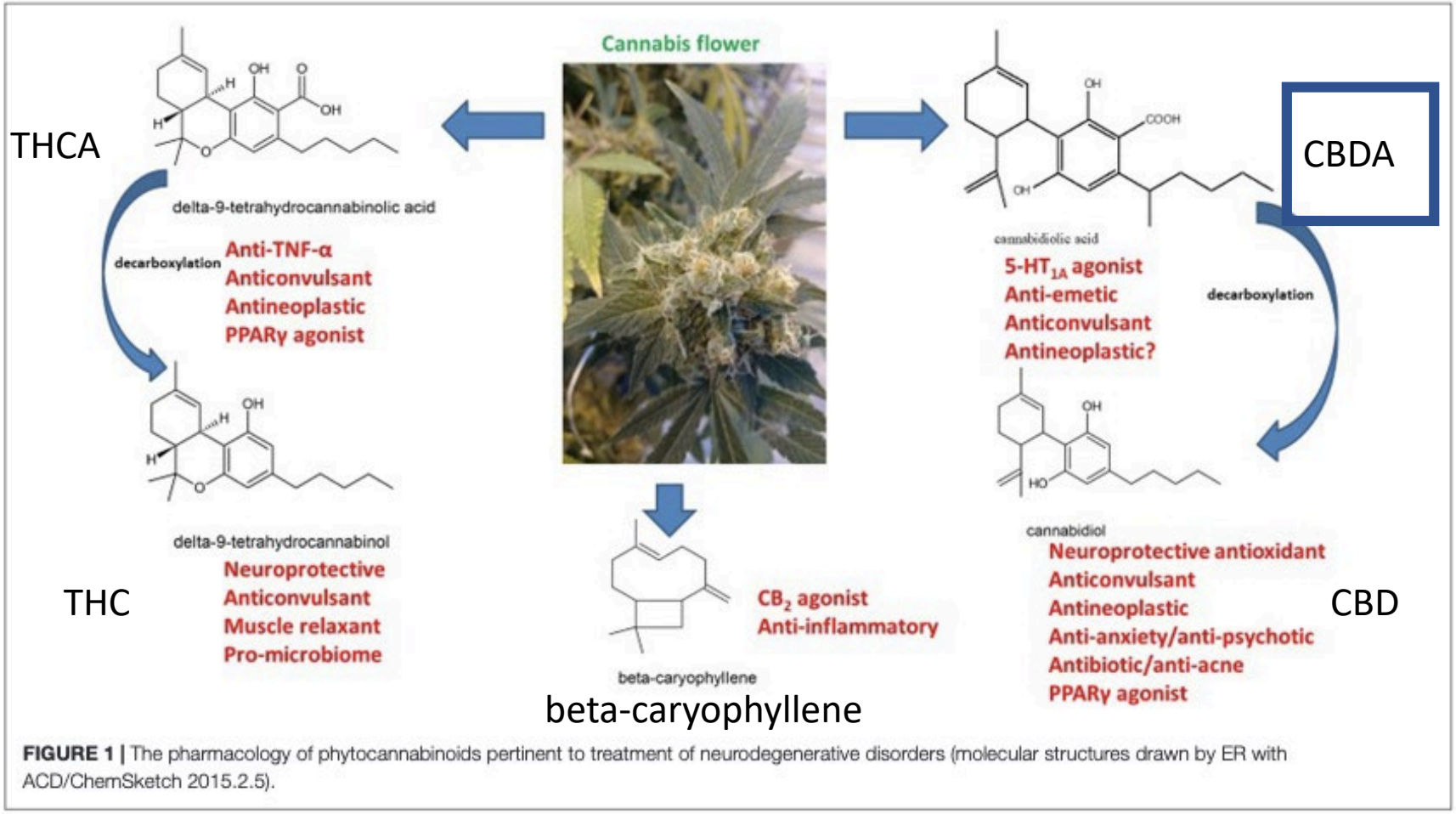
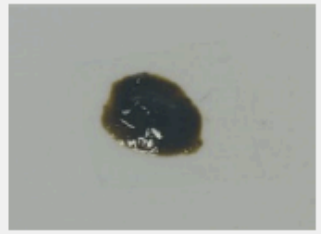


FIGURE 1 | The pharmacology of phytocannabinoids pertinent to treatment of neurodegenerative disorders (molecular structures drawn by ER with ACD/ChemSketch 2015.2.5).

CBDA – canabidiolic acid

Sample name:	5HBI
Sample type:	Paste
Batch No.:	TOM0916
Method:	PHS1M7
Date received:	29/12/2017
Date tested:	29/12/2017



- 5 children with severe epileptic encephalopathies –

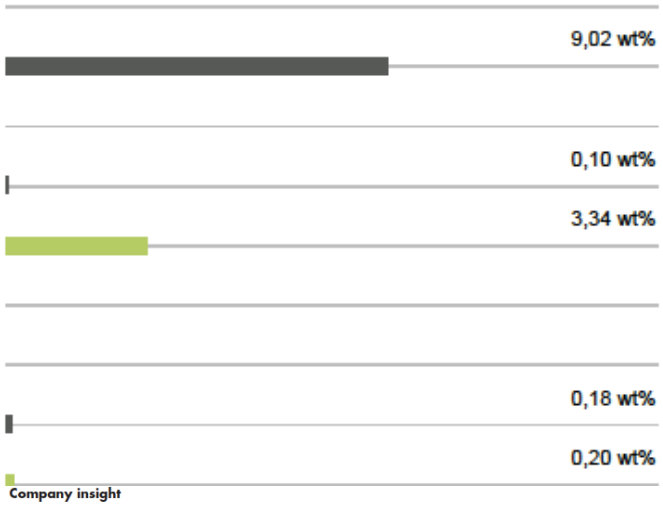
All genetically proven:

- 2 syndrome Dravet
- 1 CDKL mutation
- 1 PDHC19 mutation
- 1 Lennox-Gastaut syndrome

- ALL
  - Add-on CBDA
  - with 1 -2 AEDs + HH or CW

CANNABINOID PROFILE

	wt%	mg/g
CBDV	n/a	n/a
CBDA	9,02	90,2
CBGA	n/a	n/a
CBG	0,10	1,0
CBD	3,34	33,4
THCV	< 0.03	< 0.3
CBN	< 0.03	< 0.3
CBC	0,18	1,8
THC	0,20	2,0
THCA	0,21	2,1
TOTAL	13,05	130,5



Nearly no seizures and better cognitive functions and behavior

supplied by Pharma Hemp®

World Pharma Journal, 2019

Company insight

Add-on treatment with a hands-on approach

Dr David Neubauer of the Medical Faculty and University Medical Centre of the University of Ljubljana and of the Children's Hospital, in collaboration with **PharmaHemp**, discusses the benefits and future development of administering CBD-based medication to children.

There are more than 140 known phytocannabinoids in the cannabis plant; however, the best known are cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC). The first of these, CBD, has no negative psychotropic effects. In fact, it even works against unpleasant psychotropic, and other subjective and physical effects of THC, mediated by the CB1 receptor in humans.

Blaze a trail: new evidence on display

Today, there is compelling evidence for

Dr David Neubauer
Children's Hospital

heated or aged, CBDA decarboxylates to CBD. Found in raw cannabis, CBDA can provide numerous health benefits, thanks to its natural anti-proliferative, antioxidant, antibacterial and anti-inflammatory properties. CBDA does not stimulate the endocannabinoid system quite like its precursor does, and until now there was

CBD is now thought to treat childhood epilepsy.

The results are in: an abject improvement

All patients were treated with two standard AEDs and also received medicinal-grade cannabis products from the whole plant,

Neurodevelopmental disorders and syndromes

- CDKL5 deficiency (or atypical, early Rett syndrome) includes very resistant epileptic seizures, profound global developmental delay, gross hypotonia and profound impairment of cognitive and gross motor functions – use of full–spectrum cannabis extract showed significant improvement in all domains

- Results were promising as 570 patients (pediatric and adults) revealed efficacy of cannabidiol over placebo for improvement of seizure control as well as improvement of behavioral problems

- Dale, T., Downs, J., Olson, H., Bergin, A.M., Smith, S., Leonard, H.
Cannabis for refractory epilepsy in children: a review focusing on CDKL5 Deficiency Disorder, Epilepsy Research.2019, 151: 31-39.
- Lattanzi S, et al. Highly Purified Cannabidiol for Epilepsy Treatment: A Systematic Review of Epileptic Conditions Beyond Dravet Syndrome and Lennox–Gastaut Syndrome. CNS Drugs. 2021; 35:265–281

NEWS NEUROSCIENCE NEUROLOGY AI ROBOTICS PSYCHOLOGY ABOUT NEWSL

Home › Featured

Mouse model of Angelman syndrome

… and studies going on for other neurodevelopmental disorders, such as Rett and Pitt-Hopkins, as well as schizophrenia

CBD may alleviate seizures and benefit behaviors in people with neurodevelopmental conditions

NEUROSCIENCE NEWS × SEPTEMBER 18, 2019

FEATURED NEUROLOGY NEUROSCIENCE 4 MIN READ

NEWS NEUROSCIENCE NEUROLOGY AI ROBOTICS PSYCHOLOGY ABOUT NEWSLETTER

CBD, which is a major phytocannabinoid constituent of cannabis, has already shown to have anti-epileptic, anti-anxiety, and anti-psychotic effects.

CBD, which is a major phytocannabinoid constituent of cannabis, has already shown to have anti-epileptic, anti-anxiety, and anti-psychotic effects. The image is in the public domain.

Summary: *A single exposure to CBD reduced seizure severity and improved both motor deficits and abnormal brain activity in mouse models of Angelman syndrome.*

Source: *University of North Carolina Health Care*

A marijuana plant extract, also known as cannabidiol (CBD), is being commonly used to improve anxiety, sleep problems, pain, and many other neurological conditions. Now UNC School of Medicine researchers show it may alleviate seizures and normalize brain rhythms in Angelman syndrome, a rare neurodevelopmental condition.characterized by intellectual disability, lack of speech, brain rhythm dysfunction, and deleterious, often drug-resistant epilepsy

Neuroscience news, September 2019

Our own experiences (not published)

- In clinical practice we have been using either purified cannabidol or full-spectrum cannabis extract for children with syndromes:
- Rett[A], Angelman[A], Pitt-Hopkins[A], PDCH19[A], Prader-Will, Lamb-Shaffer, Mowat Wilson, Menkes, Kleefstra[A], Schwartz-Jampel, PhelanMc Dermid[A], Bainbridge Ropers[A], Aicardi[A], Costello[A] and syndromes with clear genetic mutations such as DYRK1A[A], WDR45[A], KCNQ3[A], SATB1[A] ,TUBA1A, EHMT1 and PNKD and found

Better seizure control, better appetite, better sleep and better control of behavioral problems and temper tantrums

---

[A] = also very much expressed autistic features

Autism and related behavioral problems

- Israeli authors published in October 2019 short report on significant improvement of behavior on 60 autistic children when treated with whole plant extracts that contain CBD and THC in a 20:1 ratio, dissolved in olive oil (starting CBD dose was 1 mg/kg/day, maximal CBD dose was 10 mg/kg/day). Improvement or very much improvement was found in 61% of autistic children with severe behavioral problems.

- Same authors later confirmed on a larger study (150 children) in 2021 again (whole-plant cannabis extract containing cannabidiol and Δ9-tetrahydrocannabinol at a 20:1 ratio vs. purified cannabidiol and Δ9-tetrahydrocannabinol at the same ratio)

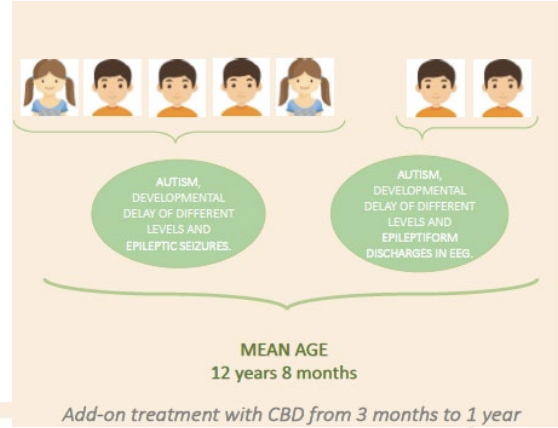
... that a whole-plant extract which contains CBD and THC in a 20:1 ratio, improved disruptive behaviors on one of two primary outcome measures with acceptable adverse events. These data suggest that cannabinoids should be further investigated in ASD.

- Aran A, Cassuto H, Lubotzky A, Wattad N, Hazan E. Brief report: Canabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems – A retrospective feasibility study. J Autism and Dev Dis. 2019;49: 1284-8.
- Aran A, Harel M, Cassuto H, Polyansky L, Schnapp A, Wattad N, Shmueli D, Golan D, Castellanos FX. Molecular Autism. 2021;12:6-13.

Univerza v Ljubljani
Medicinska fakulteta
1919 2019

univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

OUR FIRST EXPERIENCE WITH CANNABIDIOL USE IN CHILDREN WITH EPILEPSY AND AUTISM SPECTRUM DISORDER



CLINICAL GLOBAL IMPRESSION – improvement

	BEHAVIOUR	SLEEP	APPETITE	notes
average score	4.4	4.0	3.1	
	4	4	1	
	4	4	1	
	7	4	4	*Severe behavioral disorders. Referred to a psychiatrist. Connection to CBD is questionnable.*
	3	4	4	
	4	4	4	
	4	4	4	*No seizures since February.*
	5	4	4	

In all patients the frequency of epilepsy seizures decreased by 25–75%.

Four patients were seizure-free at the time of the survey.

Parental opinion was that the improvement of epilepsy in children with ASD was very good.

Parental assessment of behavior, sleep and appetite according to the CGI-I scale showed little to no change.

Our small study with CBD did not confirm these results

Our ongoing study with medicinal cannabis (CBD:THC 10:1)

- 15 children with autism and severe behavioral problems
- Starting dose of THC 0,01 mg/kg per day, gradually increasing up to 0,3 mg/kg per day
- Max. 1 mg/kg/day
- Before start: Global Clinicial Impression (GCI) – severity scale and CARS

- after: GCI – Improvement and PASS: Parental Satisfaction Survey

- Study period: 6 – 8 weeks

Preliminary results are very promising

Cerebral palsy (CP) and spasticity

- German study of Dronabinol (synthetic THC) use in children with severe forms of CP and other spasticity syndromes revealed significant improvement with the doses of 0,02 to 0,8 mg/kg/day (median: 0,47mg/kg/day), and max. 1 mg/kg/day. Side effects rare: vomiting and restlessness.
- Israeli authors used natural cannabis extracts (CBD:THC 20:1 vs. 6:1) and found regardless of the ratio:

  improvement of spasticity and dystonia,

  better sleep,

  less pain and

  improvement of quality of life.

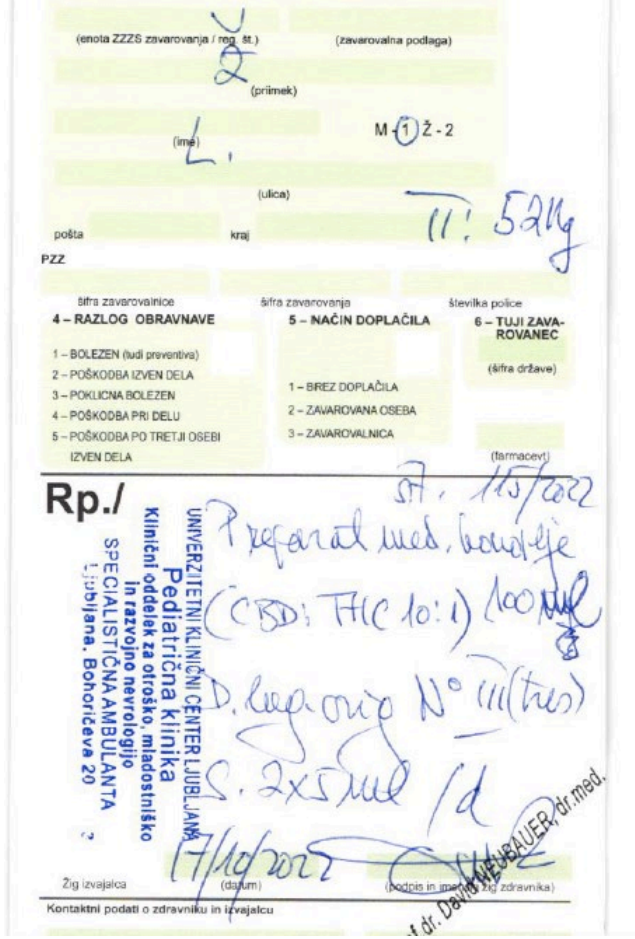
- Kuhlen M, Hoell JI, Gagnon G te al. Effective treatment of spasticity using dronabinol in paediatric palliative care. Eur J Paediatr Neurol 2016;20: 898-903.
- Libzon S, Schleider LBL, Saban N, et al. Medical Cannabis for Pediatric Moderate to Severe Complex Motor Disorders. *Journal of Child Neurology*. 2018;33(9):565-571.

Our study (still ongoing)

- For research purposes, we used a magistral preparation of full spectrum cannabis oil (FSCO), with a THC: CBD ratio of 1:10.
- The magistral preparation was prepared by the pharmacy of the UMCL from raw materials produced by the company PharmaHemp.
- The raw materials are checked at the UMCL pharmacy for content and traceability. The UMCL pharmacy agrees to the use of the magistral preparation in a clinical trial that will take place in the same institution, accordingly with regulations of clinical trials in the European Union.
- For placebo, we used MCT oil of similar color, smell and taste as a preparation of cannabinoids of plant origin.

Doses

- Starting dose of THC 0,08 mg/kg x 2
- targeted dose of THC 0,33 mg/kg x 2
- Max. dose of THC 1 mg/kg/day
- 6 - weeks


(enota ZZZS zavarovanja / reg. št.) (zavarovalna podlaga)
(priimek)
M 1 Ž - 2
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pošta kraj
PZZ
11: 5.2kg
Šifra zavarovalnice Šifra zavarovanja Številka police
4 – RAZLOG OBRAVNAVE
1 – BOLEZEN (ludi preventiva)
2 – POŠKODBA IZVEN DELA
3 – POKLICNA BOLEZEN
4 – POŠKODBA PRI DELU
5 – POŠKODBA PO TRETJI OSEBI IZVEN DELA
5 – NAČIN DOPLAČILA
1 – BREZ DOPLAČILA
2 – ZAVAROVANA OSEBA
3 – ZAVAROVALNICA
6 – TUJI ZAVAROVANEC
(šifra države)
(farmacevt)
Rp./
Preparat med. konoplje (CBD: THC 10:1) 100ml
D. lege artis N° III (tres)
S. 2x5 gtt /d
UNIVERZITETNI KLINIČNI CENTER LJUBLJANA
Pediatrična klinika
Klinični oddelek za otroško, mladostniško in razvojno nevrologijo
SPECIALISTIČNA AMBULANTA
Ljubljana, Bohoričeva 20
17/10/2022
Žig izvajalca (datum) (podpis in žig zdravnika)
Kontaktni podati o zdravniku in izvajalcu

- Physiotherapist assessed Modified Ashworth scale and GMFM before and after

Preparation supplied by Pharma Hemp®

Study characteristics

Characteristics	FSCO (n=25)	Placebo (n=15)
Sex, n (%)		
Male	16 (64%)	9 (60%)
Female	9 (36%)	6 (40%)
Age (year) - range , mean (median)	5 - 25 15,6 (14,5)	?
BMFCS level, n (%)		
IV	13 (52%)	4 (26%)
V	12 (48%)	11 (74%)
Concomitant antiseizure drugs, n (%)	19 (76%)	10 (66%)
Concomitant antispastic drugs, n (%)	16 (64%)	5 (33%)
CBD before trial start	9 (36%)	4 (26%)

GMFCS level IV and V

Results are promising

Conclusions and further perspectives

- Public is very much interested in therapeutic use of cannabis
- For the scope of Paediatrics in it is especially true for this field where conventional/classical treatment does not exist at all or is very ineffective and these are the main reasons why parents seek other therapeutic approaches or at least means for improvement of the quality of life for their children.
- Most research (evidence – based) has been done on resistant childhood epilepsies and today we have firm proof of effectiveness of cannabidiol alone (as well as of natural medicinal cannabis products) and its long-standing effect.
- Side effects are rare - like drowsiness and lack of appetite and decrease after adjusting the dose.
- Less evidence exist for the fields of autism and related disorders and spasticity (cerebral palsy) but such studies are ongoing.

Russo EB. Cannabis therapeutics and the future of neurology. Front Integr Neurosci. 2018;12:51, 1-11.
Aran A, Cayam-Rand D. Medical cannabis in children. Rambam Maimonides Medical Journal. 2020;11(1):1-10.