Klinični izsledki zdravlenja s kanabinoidi v otroški nevrologiji

Clinical results of treatment with cannabinoids in Child Neurology

Prof. David Neubauer, MD, PhD
Paediatrician & Child Neurologist
University Children’s Hospital Ljubljana
University of Ljubljana, Faculty of Medicine,
Institute ICANNA, Ljubljana
SLOVENIA

Raziskave medicinske konoplje obetajo nove paradigme zdravljenja v svetu in pri nas
Ljubljana, Hiša EU, 5. december 2022

Vsebina

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

Current scientific evidence for efficacy:

- painful HIV-associated sensory neuropathy
- chronic pain
- Chemotherapy-induced nausea & vomiting
- Addiction
- Neonatal hypoxic-ischaemic encephalopathy
- Neuropathic pain
- Anxiety
- Behavioral problems, neurodevelopmental sy.
- Intellectual disability/autism
- Seizures & Epilepsy (DEE, different syndromes)
- spams in patients with cerebral palsy
It all started with the story of small girl Charlotte who had Dravet syndrome and > 200 seizures daily

> 2014
Resistant epilepsies* and epileptic syndromes*

- Purified 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


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

- 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. Patient, 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 originalni 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 izdelava sintetičen pripravek, ki vsebuje CBD/THC v razmerju 20:1; prilagoditev odmerka po shemi
4. Pacientu, ki je jemljal lekarniški ali farmaceutski CBD in bi rad nazaj na bCBD, se to odveta, če pa pacient vztraja, se odmerke prilagodi po shemi

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, then 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
Ethical approval already in 2013

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 diary, 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

**COMIŠIJA REJEPUBLIČNE ZA MEDICINSKO ETICO**

Dr. Mirjana Perkovič Benedik, dr. med.
KO za otroško, mladozdravilo in razvojno neurologijo
Pediatriska klinika, Univerzitetni klinični center Ljubljana
Bolončeva 20, 1525 Ljubljana

Št.: 103/10/13
Dnevo: 18-11-2013

Spoštovana gospa dr. Perkovič Benedik,
Komisiji za medicinsko etiko (KME) se 24. 10. 2013 ponoviti v ocemo predlog raziskave z naslovom:

"Terapija z medicinskima konzidolom (kanabidiolom, brez psihomotornega THC) pri farmakoresistentnih epilepsijah pri otrocih."

KME je na seji 29. oktobra 2013 ucelila, da je raziskava etično sprejemljiva, in Vam z tem izdaja svoje soglasje. Povzetko pa Ves za sporočanje o rezultatih in nedeljnih pojavih.

Lep pozdrav,

prof. dr. Jože Trstenik
predsednik Komisije #5 za medicinsko etiko
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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure-free</td>
<td>14 (21.2%)</td>
</tr>
<tr>
<td>&gt;90% improvement</td>
<td>7 (10.6%)</td>
</tr>
<tr>
<td>75%-90% improvement</td>
<td>8 (12.1%)</td>
</tr>
<tr>
<td>50%-75% improvement</td>
<td>3 (4.5%)</td>
</tr>
<tr>
<td>25%-50% improvement</td>
<td>9 (13.6%)</td>
</tr>
<tr>
<td>&lt;25% improvement</td>
<td>10 (15.2%)</td>
</tr>
<tr>
<td>No improvement</td>
<td>15 (22.7%)</td>
</tr>
<tr>
<td>Worsening of seizures</td>
<td>None</td>
</tr>
</tbody>
</table>

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

> 50% reduction in 48.5% children

ID = intellectual disability, DQ = developmental quotient, BPN = bronchopneumonia
Our study – side effects

- 1x adynamic, floppy, not able to walk but dose 20mg/kg/d;
- 1x eosinophils – 8%
- 1x yellowish skin discoloration
- 1x enuresis and looks sedated (at a dose of 1000 mg/d)
- 1x 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 joyful: 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
Cannabidiol as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome

S. Lattanzi et al.

10% seizure-free
45% > 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

S. Lattanzi et al. 2017 (13) 272 patients with TLE  Arterial or subcutaneous CBD and other related products (CBD, THC, THCA)

S. Lattanzi et al. 2015 (60) 70 patients with TLE  Medicated THC duration: 2 range (1-14) 14 mg/kg/day

Presset et al. 2015 (59) 75 patients with TLE  Oral cannabidiol extract (CBD-only: n=32; CBD + other oral cannabidiol extract: n=8; THC-only: n=5; other: n=10)  Mean treatment duration: 5.5 (range 1.4-24) months

14.9% seizure-free 44% > 50%

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 36 patients with EEG data prior to and during treatment, 3 (10%) had an improvement in interictal background (desynchronisation in spike-wave discharges, improvement in background slowing). None of the 8 responders with EEG data had any interictal improvement, improvements in behaviour/attenuation (33%), language (1%) and motor skills (1%) were also reported.

Treatment was discontinued in 11 (31%) 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 (88%) and 3/12 (25%) patients with LGS and DS achieved a >50% reduction in seizure frequency.

The most common AE in the CBD group was sedation, observed in 4% of patients (all taking concomitant CBD). Increased alertness and improved verbal interaction were reported in 14% of patients on CBD and 6% of patients on CBD + CLB. The response to CBD was expected to be independent of concomitant CLB use, although CLB contributed to sedation

LGS reduction in baseline seizure frequency was achieved by 58% of children who received CBD alone, 52% of those who received CBD + CLB and 46% in the CLB group.

seizure free: from 3% to 24% 48.5% > 50% 3% seizure-free 33% > 50%

10% seizure-free 45% > 50%

21.2% seizure-free 48.5% > 50% 2.2% seizure-free 33% > 50%
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

Dose: 3-5 mg/kg/d

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

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

THCA → CBDA

THC → beta-caryophyllene

CBD
CBDA – canabidiolic acid

- 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

Nearly no seizures and better cognitive functions and behavior
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.


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

CBD, which is a major phytocannabinoid constituent of cannabis, has already shown to have anti-epileptic, anti-anxiety, and anti-psychotic effects. A single exposure to CBD reduced seizure severity and improved both motor deficits and abnormal brain activity in mouse models of Angelman syndrome.

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.
Our own experiences (not published)

• In clinical practice we have been using either purified cannabidiol or full-spectrum cannabis extract for children with syndromes:

• Rett\textsuperscript{A}, Angelman\textsuperscript{A}, Pitt-Hopkins\textsuperscript{A}, PDCH19\textsuperscript{A}, Prader-Will, Lamb-Shaffer, Mowat Wilson, Menkes, Kleefstra\textsuperscript{A}, Schwartz-Jampel, PhelanMc Dermid\textsuperscript{A}, Bainbridge Ropers\textsuperscript{A}, Aicardi\textsuperscript{A}, Costello\textsuperscript{A} and syndromes with clear genetic mutations such as DYRK1A\textsuperscript{A}, WDR45\textsuperscript{A}, KCNQ3\textsuperscript{A}, SATB1\textsuperscript{A}, TUBA1A, EHMT1 and PNKD and found

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

\textsuperscript{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.


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 Clinical 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: 0.47 mg/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.


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

- Physiotherapist assessed Modified Ashworth scale and GMFM before and after
# Study characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FSCO (n=25)</th>
<th>Placebo (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (64%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (36%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Age (year) - range, mean (median)</td>
<td>5 - 25</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>15.6 (14.5)</td>
<td></td>
</tr>
<tr>
<td>BMFCS level, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>13 (52%)</td>
<td>4 (26%)</td>
</tr>
<tr>
<td>V</td>
<td>12 (48%)</td>
<td>11 (74%)</td>
</tr>
<tr>
<td>Concomitant antiseizure drugs, n (%)</td>
<td>19 (76%)</td>
<td>10 (66%)</td>
</tr>
<tr>
<td>Concomitant antispastic drugs, n (%)</td>
<td>16 (64%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>CBD before trial start</td>
<td>9 (36%)</td>
<td>4 (26%)</td>
</tr>
</tbody>
</table>

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.