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

Michal Tzadok [a,1,*], Shimrit Uliel-Siboni [b,1], Ilan Linder [c], Uri Kramer [b], Orna Epstein [d], Shay Menascu [b], Andrea Nissenkorn [a], Omer Bar Yosef [a], Eli Hyman [d], Dorit Granot [e], Michael Dor [f], Tali Lerman-Sagie [c], Bruria Ben-Zeev [a]

[a] Pediatric Neurology Units of Chaim Sheba Medical Center, Tel Hashomer
[b] Pediatric Neurology Units of Tel Aviv Sourasky Medical Center, Tel Aviv
[c] Pediatric Neurology Units of Wolfson Medical Center, Holon
[d] Pediatric Neurology Units of Assaf Harofeh Medical Center, Zrifin
[e] Pediatric Neurology Units of Panaxia Medical Devices and Pharmaceuticals, Tel Aviv, Israel
[f] Pediatric Neurology Units of Medical Cannabis Unit, Ministry of Health, Tel Aviv, Israel

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ABSTRACT

Purpose: To describe the experience of five Israeli pediatric epilepsy clinics treating children and adolescents diagnosed as having intractable epilepsy with a regimen of medical cannabis oil.
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 20 mg/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: 13 (18%) reported 75–100% reduction, 25 (34%) reported 50–75% reduction, 9 (12%) reported 25–50% reduction, and 19 (26%) reported <25% reduction. Five (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.
Conclusions: The results of this multicenter study on CBD treatment for intractable epilepsy in a population of children and adolescents are highly promising. Further prospective, well-designed clinical trials using enriched CBD medical cannabis are warranted.

1. Introduction

About one-third of patients with epilepsy suffer from drug-resistant disease defined as failure to stop all seizures after an adequate trial of at least two appropriate medications. The efficacy of current medications in these cases is limited [1–3]. There is great interest in the development of new medications which may have antiepileptic properties, particularly those agents that affect novel receptors.

The two main cannabis ingredients with central nervous system (CNS) activity are psychoactive Δ9-tetrahydro-cannibinol (THC) and the non-psychoactive cannabidiol (CBD). THC directly activates the brain endocannabinoid system, which has a role in synaptic communication [4]. CBD is a cannabinoid receptor antagonist that modulates the endogenous cannabinoid system by potentiating intrinsic anandamide-mediated neurotransmission. In addition, CBD is involved in the regulation of other cerebral neurotransmitters and receptors, as well as having an anti-inflammatory and

* Corresponding author at: Pediatric Neurology Unit, Edmond & Lili Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel. Tel.: +972 35302687; fax: +972 35305031.
E-mail address: Michal.tzadok@gmail.com (M. Tzadok).
[1] Equal contribution to this work.

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antioxidant properties [5,6]. The mechanism of action of CBD is not well understood, but it has become clear that its anticonvulsant properties do not involve a cannabinoid receptor (CBR)-dependent mechanism [7]. Because of its multiple targets and high toxicity threshold, it is currently being investigated as a potentially useful therapeutic drug in several CNS and extra-CNS disorders, including epilepsy, in both experimental models and in humans [8,9]. The effects of cannabis on epilepsy were described by detailed case reports in the medical literature from as early as the 19th century [10,11]. Those articles were followed by several epidemiological studies that claimed a protective effect of marihuana smoking against seizures [12–14]. CBD was also found to have positive effects on seizure threshold, severity and lethality in several epilepsy mouse and rat models [15–18]. Several small controlled studies on the effect of purified CBD (200–300 mg/d) on epilepsy in adults were conducted in the 1970s [19–22]. While the first two claimed a significant effect of CBD on seizure frequency, the last two did not show any benefit for CBD use over placebo. These reported studies were analyzed in a Cochrane review [23] that concluded that because of the quality of the studies, the only answered question was the secondary outcome measure related to adverse effects and concluded that 200–300 mg/d cannabidiol had been safely administered to small numbers of patients for short time periods.

The last three years have witnessed growing interest among the medical community, parent groups and media in the use of enriched CBD medical cannabis and pure CBD in intractable pediatric epilepsy. Based on anecdotal reports and parental pressure, marijuana is currently licensed for seizures or epilepsy in 14 states in the US [24].

Medical cannabis in various ratios of CBD and THC and in different preparations (modes of administration) is licensed by the Israeli Ministry of Health (MOH) for a number of indications, including oncology-related pain and side effects of chemotherapy, phantom pain, and pain related to multiple sclerosis, diabetic neuropathy, spinal cord injury, post-traumatic stress disorder. severe intractable Gille de la Tourette syndrome, intractable epilepsy in pediatric and adult patients, intractable Crohn's disease and selected cases of severe fibromyalgia. Contraindications for its administration include a history of drug abuse, significant psychiatric background and congestive heart failure. Only experts in each specific field are allowed to apply for a license to access a special unit in the MOH by means of computer-based application forms. Each application is reviewed, and approval is given for a period of 6 months to 1 year if considered appropriate by a group of 30 key leaders in these fields of expertise nominated by the MOH and signed by one designated MOH expert physician. There are currently 23,500 active licenses in the MOH registry (200 for children with epilepsy). The cannabis preparations (oil, cigarettes, inhalation extract or flowers) are produced by 8 MOH-certified growers and distributed by them to the licensed patients through specific distribution points and accompanied by personal guidance for their proper use. Treatment follow-up is performed by the applying physician.

Our objective in this paper is to present the experience of four pediatric epilepsy units in Israel that treat children and adolescents diagnosed as having intractable epilepsy with enriched CBD medical cannabis.

2. Materials and methods

2.1. Subjects

We conducted a retrospective study based on clinical records of clinic and phone call visits of children and adolescents with refractory epilepsy who were being treated in four pediatric epilepsy centres in Israel. The participating clinics are all tertiary referral centers for pediatric epilepsy in Israel, and each treats thousands of patients with epilepsy, including many with intractable disease. All the patients that received CBD-enriched cannabis oil (CECO) were followed by each of the clinics for at least 12 months before receiving CECO. It was offered to them by the physician after they had been resistant to 5–7 drugs, or treatment by a ketogenic diet or vagal nerve stimulation (VNS). The possibility of CECO was also raised by the child's parents who learned about that treatment option via information made available by the media. One pediatric neurologist followed the patients in each clinic.

The cohort included children who were treated with cannabis oil for more than 3 months throughout 2014. Patients aged 1–18 years with refractory epilepsy that was characterized by daily seizures refractory to >7 appropriate antiepileptic drugs (AEDs) and other treatment modes, i.e., VNS 35/74 (47%), epilepsy surgery 3 (4%), and ketogenic diet 29/74 (39%) were included. Patients with severe behavioral disorders and significant family psychopathology were excluded.

The study patients were divided into six groups based on seizure etiology:

1. Acquired
2. Early epileptic encephalopathy with a known genetic etiology
3. Epileptic encephalopathy without a known genetic etiology
4. Congenital brain malformations
5. Hypoxic ischemic encephalopathy
6. Other (etiology not defined)

2.2. Study medication

CBD-enriched cannabis oil was supplied by two licensed growers (Better and Tikun Olam, Tel-Aviv, Israel), and the preparation of the oil was made by two methods. In the first method, the cannabis plant material was extracted in PhEur absolute ethanol, followed by evaporation and decarboxylation. The concentrate was diluted in PhEur canola oil to the required concentration of 20% CBD and 1% THC. Preservatives and antioxidants were added to ensure stability of the active ingredients. The ingredient concentration and quality analysis was done four times by high performance liquid chromatography (HPLC) during the different stages of the preparation process. In the second method, the cannabis oils were extracted from two CBD-rich cannabis strains using ethanol as an extracting solvent. The preparation at the crude extract level, the purified CBD and the final solution level were analyzed by both HPLC and gas chromatography-mass spectrometry. The ratio between THC and CBD was standardized and corrected to 20:1 by the addition of pure CBD. At the final stage, the preparations were assayed to ensure the absence of fungi and molds (based on the Israeli Standard 885 for preparation sterility). The CBD and THC analyses were performed in two independent labs which supply services for the growers. One is a university lab and the other is a GMP-approved lab.

The CBD dosage ranged from 1 to 20 mg/kg/d, and it was divided into two groups, 1–10 mg/kg/d and 10–20 mg/kg/d. The final dose used for each patient was defined according to seizure response and side effects. The THC dosage did not exceed 0.5 mg/kg/d, which is considered far below the safety margin of THC. In some cases, the patient's other medications were reduced if there was decrease in seizure frequency and adjusted according to side effects, in addition to drug level adjustments while on CECO. Seizure reduction was rated according to four levels (0%, <25%, 25–50%, 50–75%, and 75–100%) as reported by parents and older patients. Parents were asked to report the number of seizures per period and we did the percentage calculations. Side effects were also reviewed.

The study was approved by the IRB committee of the four participating centers.

3. Results

A total of 74 patients met the study inclusion criteria. One-half of them (37/74, 50%) were younger than 10 years of age. Sixty-five (88%) of the patients were cognitively impaired as follows: mild 16/74 (22%), moderate 14/74 (19%), and severe 34/74 (46%), with only 10 of them (13%) having normal cognition. The CECO treatment duration was between 3 and 12 months. The median duration of exposure was 5.5 months and the duration of follow-up was 10 months. The CBD dosage ranged from 1 to 20 mg/kg/d: 60 (81%) patients were treated with <10 mg/kg/d of CBD and 14 (19%) treated with >10 mg/kg/d of CBD, with the highest CBD dose reaching 270 mg/day.

Most of the patients (66/74, 89%) reported some reduction in seizure frequency: 13 (18%) had 75–100% reduction, 25 (34%) had 50–75% reduction, 9 (12%) had 25–50% reduction, and 19 (26%) had <25% reduction. Five (7%) patients reported aggravation of seizures which led to withdrawal of the cannabis oil.

One patient, a 7-month-old with severe acquired hypoxic ischemic damage, intractable spasms and partial complex seizures, became seizure-free on CECO at a dosage of 2 mg/kg/d. The improvement demonstrated on his electroencephalogram (EEG) enabled a gradual decrease in the dosages of his other antiepileptic drugs (AEDs).

The results of cannabis oil treatment according to seizure etiology are displayed in Table 1. In the first two groups (epileptic encephalopathies with or without known genetic mutations), 66% (30/45) of the children showed more than a 25% reduction in seizure frequency, with 23/45 (51%) reporting between 50 and 100% reduction in seizure frequency. Table 2 lists the results of cannabis oil treatment according to dosage. Positive effects not related to seizure frequency were reported by 44/74 patients, and they included improved behavior and alertness in 25/44, improved language, communication and motor skills in 11/44, and improved sleep in 8/44.

Adverse events were reported by 34/74 patients (Table 3). The side effects led to the withdrawal of medical cannabis in five patients.

4. Discussion

The use of enriched CBD oil in the treatment for intractable pediatric epilepsy patients is becoming increasingly popular. Three publications on retrospective studies appeared between 2013 and 2015 describing parental surveys or the experience of epilepsy clinics with enriched CBD oil among various pediatric epilepsy populations [25–27]. Although they showed a favorable effect of CBD-enriched cannabis in the pediatric epilepsy population, those reports lacked objectivity as well as crucial data on the study population and on the compounds used according to varying considerations. The first was a retrospective study that described a telephone/Internet survey of 19 parents whose children had various childhood epileptic encephalopathies for which they received CBD-enriched medical marijuana: 16 (84%) had a reduction in seizure frequency and two became seizure-free [25]. The second report was a retrospective chart review from a single tertiary epilepsy center, and it included 75 children and adolescents with various epileptic encephalopathies who were given medical cannabis [26]. Thirty-three percent reported a >50% reduction in seizures, while 57% reported some improvement in seizure control. The response rate was syndrome-dependant: Dravet syndrome had a rate of 23%, Doose syndrome 0%, and Lennox–Gastaut syndrome 88.9%. No benefit was demonstrated in the available EEGs. The third report was an online parental survey that focused on perceived efficacy, dosage, and tolerability of CBD-enriched cannabis preparations for children with infantile spasms and Lennox–Gastaut syndrome and other intractable epilepsies. A total of 117 parents responded to the survey. The perceived efficacy and tolerability were similar across etiologic subgroups, with 85% reporting some reduction in seizure frequency and 14% reporting complete seizure freedom. The median duration and the median dosage of CBD exposure were 6.8 months and 4.3 mg/kg/day, respectively [27]. The few side effects reported in these three studies included increased appetite, somnolence/fatigue, and an increase in seizure frequency [25–27]. Rare adverse events were developmental regression, abnormal movements, status epilepticus requiring intubation, and death. The beneficial effects other than seizure control that were reported in all three studies by parents included sleep quality improvement, increased alertness, and better mood during CBD therapy. Improvements in language and motor skills were reported in 10% of patients in a study by Hussain et al. [27].

Our current investigation is a large retrospective study. It differs from the previously reported studies [25–27] in a number of aspects. The patients and their epilepsy course were well known to the treating physicians in all four participating centers. Only two CBD-enriched cannabis solutions with known and well-controlled compositions were used, and the titration of dosage was done regularly by the treating physician according to seizure response and side effects during clinic visits. The follow-up was done mainly in person with additional in-between phone calls and not by printed questionnaires, which may strengthen the reliability of the data. Because of the novelty of using medical cannabis in pediatric epilepsy, the physicians were very selective in their inclusion criteria and chose only patients with severe refractory epilepsy

Table 1
Results according to seizure etiology.

	Seizure reduction				
	0% no. of cases	<25% no. of cases	25–50% no. of cases	50–75% no. of cases	>75% no. of cases
Known genetic mutation	2	9	2	8	4
Unknown genetic mutation	0	4	5	8	3
Acquired	1	1	1	2	3
Brain malformation	0	1	0	1	1
Hypoxic ischemic	4	1	1	5	0
Others*	1	3	0	1	2
Total	8 (11%)	19 (26%)	9 (12%)	25 (34%)	13 (17%)

Table 2
Seizure reduction according to dosage.

Dosage	0% no. of cases	<25% no. of cases	25–50% no. of cases	50–75% no. of cases	>75% no. of cases	Total no. of cases
<10 mg/kg/d	4	14	8	24	10	60 (81%)
>10 mg/kg/d	4	5	1	1	3	14 (19%)

Table 3
Adverse events reported in 34/74 patients.

Adverse events	No. of cases
Seizure aggravation	13 (18%)
Somnolence/fatigue	16 (22%)
Gastrointestinal problems and irritability	5 (7%)

(i.e., all had failed at least 7 AEDs and most had also failed the ketogenic diet, VNS or epileptic surgery or both).

We divided the patients into six groups according to etiology. The largest was the group that had epileptic encephalopathy with or without a known genetic etiology (59%). While 66% of the epileptic encephalopathy group (30/45) showed more than a 25% reduction in seizure frequency, only 45% (14/31) of the other children showed a similar response rate. Importantly, there was no difference in the baseline severity of epilepsy between the groups by the physicians' clinical assessment.

Because of no previous experience and no available data on the effect and safety of CBD and the limitations related to THC dosage, three out of the four participating centres chose to titrate the cannabis oil slowly and kept the patients on a relatively low CBD dose (<10 mg/kg/d), with only 13 patients (17%) reaching a CECO dosage higher than 10 mg/kg/d. The small size of the high dose group precludes our reaching any conclusions regarding dosage-related efficacy.

Side effects of substance use were inevitable, but their rate and severity were not different from most known AEDs. There were no allergic responses. Somnolence and fatigue were relatively common but they were mostly temporary. It is also important to mention that CECO was added to at least 2 other AEDs in all patients, and that drug–drug interactions may have been the underlying cause for the fatigue and somnolence. There were no major systemic side effects, and the reported gastrointestinal problems were of minor significance. The seizure aggravation reported in 7% of the patients can be partly related to the disease's natural history. Most of our study patients were cognitively impaired, thus preventing the option to assess the effect of CECO on cognition.

Our study has several imitations, including the lack of a control group, no consistent rate of dosage elevation, reliance upon parental report on seizure frequency, short duration of the study and lack of long-term outcome, no EEG results and no measurement of other drug levels. Since it is a retrospective study, there was no planned baseline period before commencing CECO. However, because all the patients were well-known and continuously followed-up in the participating clinics, the natural history of their epilepsy was well known and served as baseline.

5. Conclusions

The results of this multicenter study on CBD enriched cannabis oil treatment for intractable epilepsy in a population of children and adolescents are highly promising. Further prospective, well-designed clinical trials using enriched CBD medical cannabis are warranted to validate our findings.

Disclosures

All authors have no commercial, financial or other associations to disclose that pose a conflict of interests I connection with the article.

Author contribution/roles

Michal Tzadok and Bruria Ben Zeev were responsible for the concept and design of the study, for the collection of data, interpretation of the data, and for the drafting and editing of the document. Shimrit Uliel-Siboni, Ilan Linder, Uri Kramer, Orna Epstein, Andrea Nissenkorn, Omer Bar Yosef, Eli Hyman, Shay Menascu, and Michal Dor were responsible for the collection of data. Dorit Granot was responsible for the drafting of the document. Tali Lerman-Sagi and Uri Kramer were responsible for editing of the document. All authors have read and have approved the manuscript as submitted. All authors are responsible for the reported research.

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