DANISH MEDICAL JOURNAL

Original Article

Dan Med J 2021;68(5):A07200527

Cannabidiol treatment of severe refractory epilepsy in children and young adults

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Dan Med J 2021;68(5):A07200527

ABSTRACT

INTRODUCTION: Since 2016, the Paediatric Department of the Filadelfia Epilepsy Hospital, Denmark, has been treating patients with cannabidiol for severe refractory epilepsy. This study describes treatment results, evaluates the effect of clobazam co-medication and compares findings in Dravet and Lennox-Gastaut patients with results in patients with other epilepsies.

METHODS: This was a retrospective cohort study including 78 patients treated with off-label cannabidiol in 2016-2019. Diagnoses, previous and concomitant treatment, and presence of motor seizures were assessed. Effect on seizures was evaluated by seizure frequency registration or perceived effect in patients without seizure frequency registration.

RESULTS: In 51 patients with seizure frequency registration, 31.4% had ≥ 50% seizure reduction at three months, 31.1% at six months, 28.1% at 12 months and 20.0% at 24 months. At the same periods, some degree of seizure reduction was: 68.6%, 57.8%, 46.9% and 20.0%, respectively. Seizure reduction was higher with clobazam co-medication. In Dravet and Lennox-Gastaut patients, 70.0% had ≥ 50% seizure reduction at three months compared with 22.0% in patients with other epilepsies, where some degree of seizure reduction at three months were 80.0% and 65.9%, respectively.

CONCLUSIONS: Cannabidiol is a treatment option in children and young adults with severe refractory epilepsy other than Dravet and Lennox-Gastaut syndromes, but close evaluation of its effects is important to taper off treatment in case a treatment effect is lacking. Clobazam co-medication increases seizure reduction.

FUNDING: none.

TRIAL REGISTRATION: not relevant.

Randomised controlled trials (RCTs) [1-3] have shown an effect of cannabidiol (CBD) treatment in epilepsy patients with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS). In December 2016, the Paediatric Department, Filadelfia Epilepsy Hospital, Denmark, commenced off-label treatment with CBD oil for severe refractory epilepsy in patients with a variety of epilepsy diagnoses. The CBD treatment was protocol based with a dosage plan, blood test intervals and seizure monitoring. This study was conducted as a quality control study of the CBD off-label treatment aiming to evaluate the results of CBD treatment of severe refractory epilepsy and to study the effect of co-medication with clobazam (CLB), since CBD is known to increase the plasma level of the active metabolite of CLB (N-desmethylclobazam, nCLB) [4]. Furthermore, the aim was to compare seizure reduction results in patients with DS or LGS (DS/LGS group) to the results seen in patients with other epilepsy diagnoses (non-DS/LGS group).

In September 2019, Epidyolex (containing CBD and no tetrahydrocannabinol (THC)) was authorised by the European Medicines Agency for use in epilepsy in addition to CLB in DS and LGS patients beyond two years of age [5]; and in June 2020, Epidyolex was introduced to the Danish market. Hence, CBD is no longer an off-label treatment in the DS/LGS group.

METHODS

This was a single-centre retrospective cohort study including children and young adults started in CBD off-label treatment from December 2016-December 2019 at the Paediatric Department, Filadelfia Epilepsy Hospital, Denmark. The inclusion criterion was severe refractory epilepsy with weekly invalidating seizures in children more than two years of age. The contraindications were hepatocellular injury, significant laboratory abnormalities, felbamate start within the past year or allergy to any of the ingredients. Patients were characterised by an epilepsy diagnosis [6], significant comorbidity, age at epilepsy debut and at CBD initiation, previous epilepsy treatment (number of antiepileptic drugs (AEDs), diet (ketogenic, modified Atkins or low glycaemic index treatment), vagus nerve stimulator (VNS), and epilepsy surgery) and concomitant epilepsy treatment (AEDs, diet and functioning VNS).

Prior to CBD treatment, blood tests with therapeutic drug monitoring (TDM), full blood count and kidney and liver function tests were obtained. Patients initiating treatment in 2016-2017 also had standard electroencephalography (EEG), and guardians filled out the Epilepsy and Learning Disability Quality of Life (ELDQOL) questionnaire [7]. CBD was initiated during admission. The magistrally produced CBD oil formulation used was 300 mg/ml made at Glostrup Pharmacy, Denmark. The oil is produced from hemp plants grown in German green houses and diluted in palmitoyl and containing no THC. Dosage titration started at 5 mg/kg/day, divided twice daily, and increased by 5 mg/kg/day every 3-5 days depending on the protocol and adverse effects (AEs). In 2018, the protocol was changed to the more rapidly incremented plan. Blood tests were repeated before discharge and two weeks after every dosage increment. The maximum CBD dosage was 20 mg/kg/day as used in the RCTs [1-3].

Seizure frequency registration (SFR) was done by the guardian by a seizure app or seizure diary with a one-month baseline (BL) registration before CBD initiation and continually hereafter. In patients without BL, where SFR was started only at CBD initiation, the first treatment month registration was used as BL. In patients without SFR, the patient files were reviewed for noted effect on seizures and registered as either “effective” (if the guardian had the impression of seizure reduction caused by CBD) or “uncertain effect/ineffective” (if the guardian had no impression of seizure reduction or the effect was not described). CBD effect on seizures was calculated or evaluated for every treatment month after CBD initiation during ongoing treatment. Some patients initiated SFR and later discontinued SFR during ongoing CBD treatment. In these cases, evaluation was continued as “effective” or “uncertain effect/ineffective”.

Patients who initiated CBD in 2016-2017 had a standard EEG and ELDQOL done about three months after CBD initiation. AEs and perceived effect on mental state and sleep were evaluated by patient-record review and ELDQOL, if present. Changes in concomitant epilepsy treatment during CBD treatment were accepted. The follow-up time for all patients was until the end of 2019, except for patients initiated from October to December 2019, for whom follow-up time was three months.

The primary outcome measures were percentage of patients with a seizure reduction on CBD treatment and the degree of seizure reduction. In patients without SFR, the outcome was “effective” or “uncertain effect/ineffective”. The effect of CLB co-medication was compared with non-CLB both in patients with and without SFR. The effect of CBD on seizure reduction in the DS/LGS group was compared with the non-DS/LGS

group in patients with SFR.

The secondary outcome measures were AEs, changes in TDM and other paraclinical measures, effect of CBD treatment on EEG, perceived effect on mental state and sleep, and causes of CBD discontinuation. The two-tailed unpaired t-test was used to compare means. Fisher's exact test was used to compare differences in proportions between groups. The level of significance was set at $p < 0.05$.

Trial registration: not relevant. Journal information was obtained pursuant to the Danish Health Act, Section 42d, subsection 2, no. 2, barring cases in which a guardian specifically requests that patient information not be used for quality work.

RESULTS

Study population

A total of 79 patients initiated off-label CBD treatment from December 2016 to December 2019. One patient was not included due to a specific guardian request. Hence, 78 patients were evaluated (total patient group, n = 78). The follow-up time was 3-36 months, median 15.2 months. One patient who initiated CBD due to a continuous spike-wave during slow-wave sleep was not included in the evaluation of CBD effect on seizures, since the epilepsy did not meet the inclusion criterion of weekly invalidating seizures (total seizure group, n = 77). This patient was included in the evaluation of secondary outcome measures. For study population and groups, see **Table 1**. Patients predominantly had motor seizures (Table 1). No significant differences were found between the DS/LGS group (n = 15) and the non-DS/LGS group (n = 62) regarding age at epilepsy debut, age at CBD initiation, previous or concomitant epilepsy treatment or motor seizures, indicating that the severity and intractability of the epilepsies were similar in the groups.

TABLE 1 Patient population characteristics. Epilepsy diagnoses, epilepsy syndromes and aetiologies, significant comorbidity, gender distribution, age at epilepsy debut, age at cannabidiol initiation, previous epilepsy treatment before cannabidiol initiation, concomitant epilepsy treatment at cannabidiol initiation, and motor seizures.

	Patients followed-up, n (%)	Median	Mean (range)
Epilepsy diagnoses, epilepsy syndromes and aetiologies			
Epileptic and developmental encephalopathy/focal, multifocal, epilepsy/combined generalised			
and focal epilepsy:			
Acquired structural cause: ischaemia, infarction, haemorrhage, meningoencephalitis, hypoglycaemia, vaccination sequelae	13 (16.7)		
Structural abnormality: cortical dysplasia, heterotopia, polymicrogyria, pachygyria, Dandy Walker malformation, Aicardi syndrome	14 (17.9)		
Rett syndrome: *MECP2* mutation, atypical Rett syndrome: *CDKL5* mutation	11 (14.1)		
Tuberous sclerosis: *TSC1* or *TSC2* mutation	2 (2.6)		
Other known genetic aetiologies: *COL4A1* mutation, *STXBP1* deletion, *ATP1A3* mutation, *STAMBP* mutation, *GRIN1* mutation, Menkes disease, Aicardi-Goutières syndrome, 12q13 deletion, 6q24.2.26 deletion, isodicentric 15, 15p24 microduplication	11 (14.1)		
Unknown aetiology	7 (9.0)		
Subtotal	58 (74.4)		
LGS: several seizure types, including tonic seizures, interictal slow spike-waves, spikes			
and bursts of 10-20-Hz spikes during sleep, and cognitive impairment [8]			
Acquired structural cause: ischaemia	1 (1.3)		
Structural abnormality: microdysplastic changes	1 (1.3)		
Known genetic aetiology: *DOCK7* mutation	1 (1.3)		
Unknown aetiology	5 (6.4)		
Subtotal	8 (10.3)		
DS: *SCN1A* mutation	7 (9.0)		
Other epilepsy types: focal epilepsy, myoclonic astatic epilepsy, GEFS+, idiopathic generalised epilepsy: childhood absence epilepsy, Rolandic epilepsy, idiopathic ESES/CSWS	5 (6.4)		
Total	78		
Significant comorbidity			
Significant psychomotor retardation, moderate or severe mental retardation, autism spectrum disorder or autistic behaviour, hyperactivity disorder, behavioural disorder, cerebral palsy with Gross Motor Function Classification System V	75 (96.2)		
Total	78		
Gender distribution			
Patient group:			
Male	38 (48.7)		
Female	40 (51.3)		
Total	78		
Age at epilepsy debut			
Total seizure group	77	0.5 yrs	1.6 (0.0-12.0) yrs
DS/LGS group	15	0.8 yrs	1.9 (0.0-12.0) yrs
Non-DS/LGS group	62	0.5 yrs	1.5 (0.0-8.5) yrs
Age at CBD start			
Total seizure group	77	10.5 yrs	10.6 (1.7-20.8) yrs
DS/LGS group	15	9.9 yrs	10.6 (4.5-18.1) yrs
Non-DS/LGS group	62	10.6 yrs	10.6 (1.7-20.8) yrs
Previous epilepsy treatment before CBD start			
Previous antiepileptic drugs:			
Total seizure group	77	10	9.8 (4-17)
DS/LGS group	15	11	10.5 (4-15)
Non-DS/LGS group	62	10	9.7 (4-17)
Previous diet: ketogenic, modified Atkins, low glycaemic index treatment:			
Seizure group, total	77		
Seizure group, previous diet	53 (68.8)		
DS/LGS group, total	15		
DS/LGS group, previous diet	12 (80)		
Non-DS/LGS group, total	62		
Non-DS/LGS group, previous diet	41 (66.1)		

Continues >

TABLE 1 CONTINUED Patient population characteristics. Epilepsy diagnoses, epilepsy syndromes and aetiologies, significant comorbidity, gender distribution, age at epilepsy debut, age at cannabidiol initiation, previous epilepsy treatment before cannabidiol initiation, concomitant epilepsy treatment at cannabidiol initiation, and motor seizures.

	Patients followed-up, n (%)	Median	Mean (range)
Previous vagus nerve stimulator treatment:			
Seizure group, total	77		
Seizure group, previous treatment	34 (44.2)		
DS/LGS group, total	15		
DS/LGS group, previous treatment	8 (53.3)		
Non-DS/LGS group, total	62		
Non-DS/LGS group, previous treatment	26 (41.9)		
Previous epilepsy surgery:			
Seizure group, total	77		
Seizure group, previous surgery	2 (2.6)		
DS/LGS group, total	15		
DS/LGS group, previous surgery	1 (6.7)		
Non-DS/LGS group, total	62		
Non-DS/LGS group, previous surgery	1 (1.6)		
Concomitant epilepsy treatment at CBD initiation			
Concomitant antiepileptic drugs:			
Total seizure group	77	2	2.5 (0-5)
DS/LGS group	15	3	2.5 (1-4)
Non-DS/LGS group	62	2	2.5 (0-5)
Concomitant diet: ketogenic, modified Atkins, low glycaemic index treatment:			
Seizure group, total	77		
Seizure group, concomitant diet	12 (15.6)		
DS/LGS group, total	15		
DS/LGS group, concomitant diet	2 (13.3)		
Non-DS/LGS group, total	62		
Non-DS/LGS group, concomitant diet	10 (16.1)		
Concomitant functioning vagus nerve stimulator treatment:			
Seizure group, total	77		
Seizure group, concomitant treatment	26 (33.8)		
DS/LGS group, total	15		
DS/LGS group, concomitant treatment	6 (40.0)		
Non-DS/LGS group, total	62		
Non-DS/LGS group, concomitant treatment	20 (32.3)		
Motor seizures: tonic, clonic, tonic-clonic, atonic, epileptic spasms, myoclonic, hyperkinetic [9]			
Seizure group, total	77		
Seizure group, motor seizures	76 (98.7)		
Seizure group, > 1 seizure type	74 (96.1)		
DS/LGS group, total	15		
DS/LGS group, motor seizures	15 (100)		
Non-DS/LGS group, total	62		
Non-DS/LGS group, motor seizures	61 (98.4)		

CBD = cannabidiol; CSWS = continuous spike-wave during slow-wave sleep; DS = Dravet syndrome; ESES = electrical status epilepticus; during slow sleep; GEFS = generalised epilepsy with febrile seizures; LGS = Lennox-Gastaut syndrome.

Table 1 has been updated on May 6th 2021 due to an error.

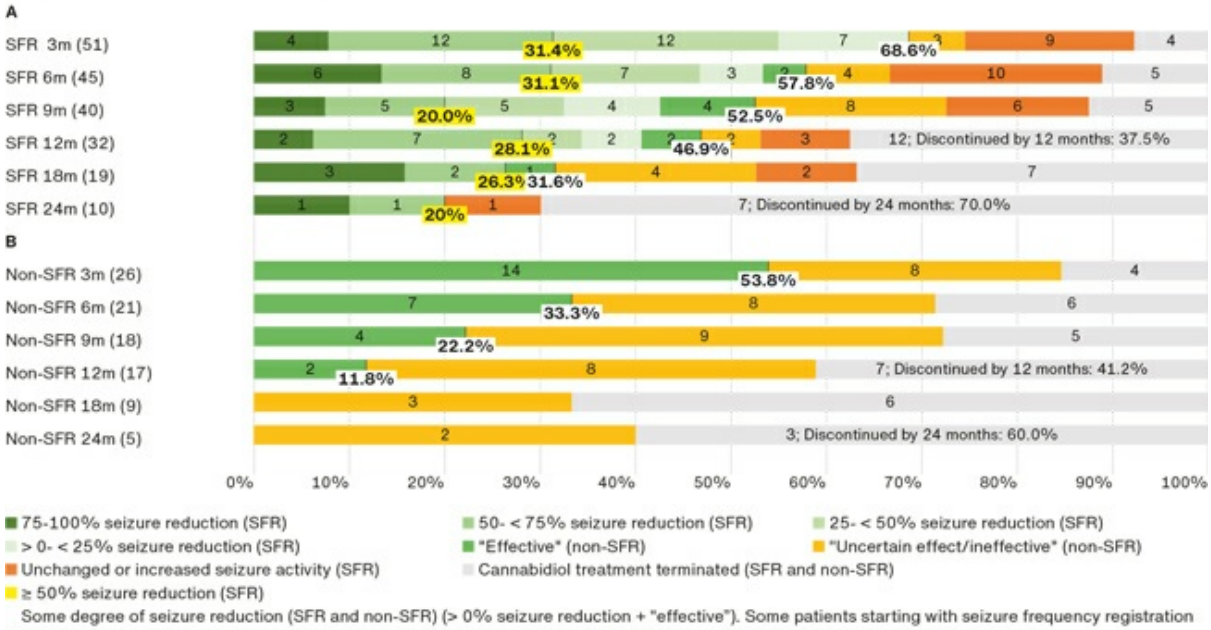
Effect on seizure activity

In the total seizure group, 46.8% (n = 36) had SFR with one-month BL and 19.5% (n = 15) had SFR with no BL (first treatment month SFR was used as BL). Patients with SFR (with and without BL) were evaluated together, SFR group, 66.2% (n = 51), since no significant differences were found between the groups (**see Supplementary figure** https://ugeskriftet.dk/files/a07200527_supplementary.pdf). In 33.8% (n = 26), no SFR was done (non-SFR group) due to lack of emphasis on SFR on the physician's part and due to a busy schedule on the guardian's part with a child with severe epilepsy and comorbidity, and SFR not being mandatory.

For effect of CBD on seizure activity in the SFR group, see **Figure 1**A. At three months, 31.4% of the patients in the SFR group had ≥ 50% seizure reduction. At 12 months, this was 28.1%. A total of 68.6% of the patients in the SFR group had some degree of seizure reduction at three months. At 12 months, this was 46.9%. For effect of CBD on seizure activity in the non-SFR group, see Figure 1B. At three months, 53.8% of the patients were

evaluated to have seizure reduction by the guardian. At 12 months, this was 11.8%.

FIGURE 1 Effect of cannabidiol treatment on seizure activity in patients with seizure frequency registration (SFR) (**A**) and in patients without seizure frequency registration (non-SFR) (**B**). Results for every third month (m) are shown in the first year of follow-up and every six m.s in the second year of follow-up. Only results until 24 m.s of follow-up are shown.



Some degree of seizure reduction (SFR and non-SFR) (> 0% seizure reduction + "effective"). Some patients starting with seizure frequency registration discontinued this, resulting in their evaluation as "effective"/ "uncertain effect/ineffective" in the seizure frequency registration group
( ): number of patients followed-up.

For CBD effect on seizure activity with and without CLB in the SFR group, see **Figure 2**A. At three months, 40.0% of patients in CLB co-medication had ≥ 50% seizure reduction compared with 25.8% of patients without CLB co-medication ($p > 0.05$). At 12 months, these numbers were 35.7% versus 22.2% ($p > 0.05$). For CBD effect on seizure activity with and without CLB in the non-SFR group, see Figure 2B. At three months, 87.5% of patients in CLB co-medication had effect on seizures compared with 38.9% of the non-CLB treated patients evaluated by the guardian ($p < 0.05$). For CBD effect on seizure activity in the DS/LGS group and the non-DS/LGS group in patients with SFR, see Figure 2C. At three months, 70.0% of patients in the DS/LGS group had ≥ 50% seizure reduction compared with 22.0% of patients in the non-DS/LGS group ($p < 0.05$).

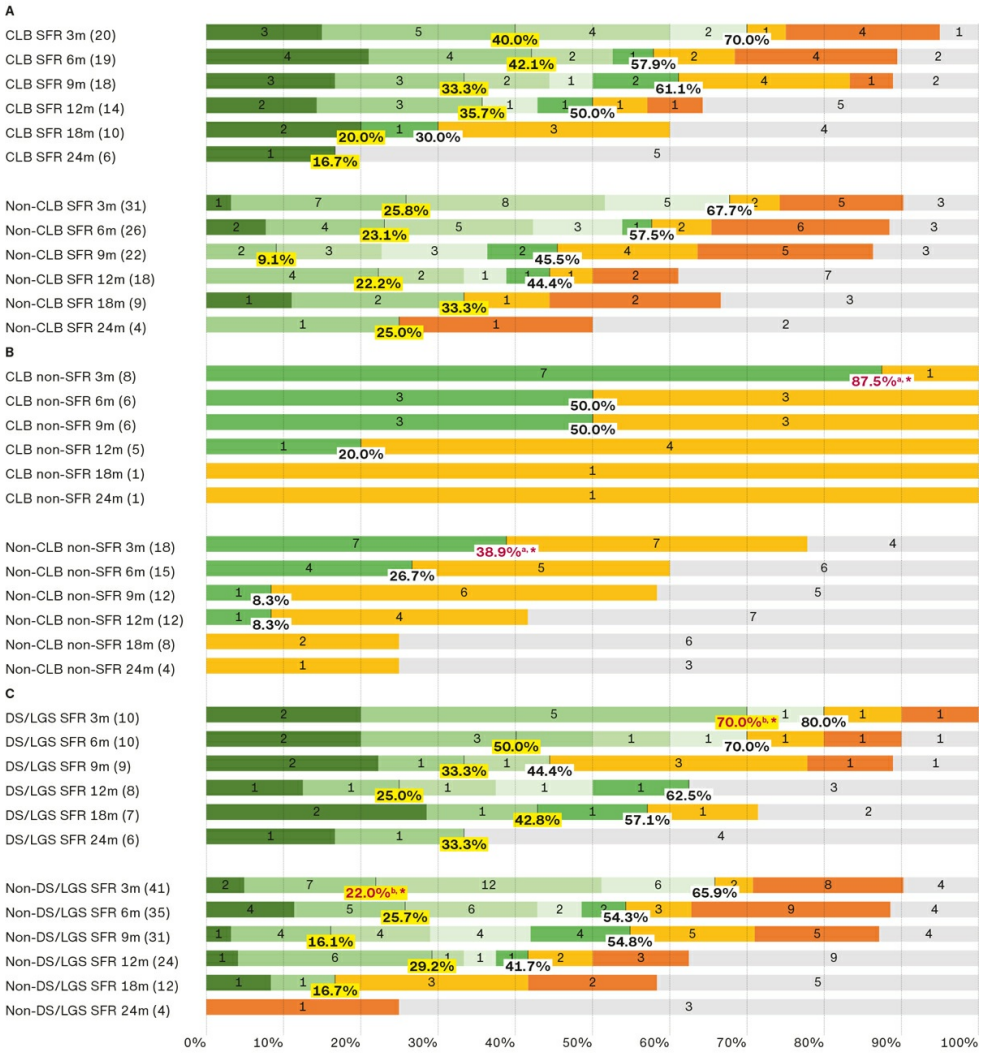


FIGURE 2 Effect of cannabidiol treatment on seizure activity in the clobazam (CLB) and non-clobazam (non-CLB) groups in patients with seizure frequency registration (SFR) (**A**) and in patients without SFR (non-SFR) (**B**). Effect of cannabidiol on seizure activity in the Dravet/Lennox-Gastaut syndrome (DS/LGS) group and in the non-DS/LGS group for patients with SFR (**C**).

CLB = clobazam co-medication group; DS/LGS = Dravet/Lennox-Gastaut syndrome group; m = months; Non-CLB = non-clobazam group; Non-DS/LSG = non-Dravet/Lennox-Gastaut syndrome group; Non-SFR = non-seizure frequency registration group; SFR = seizure frequency registration group.
( ): number of patients followed up.
*) $p < 0.05$.
a) Comparison between CLB non-SFR 3m and non-CLB non-SFR 3m.
b) Comparison between DS/LGS SFR 3m and non-DS/LGS SFR 3m.

Figure 2 har been updated on May 6th 2021 due to an error.

Adverse events

For AEs, see **Table 2**. Fatigue was the major AE of CBD and was predominantly seen on dosage increment or at high dosage. Increase in seizure activity was most frequently seen with CBD dosage ≥ 10 mg/kg/day. Verified status epilepticus with CBD as the suspected cause was seen in 2.6% of patients (n = 2) and this led to CBD termination. Patients in CLB co-medication had a higher risk of certain AEs, i.e. fatigue and behavioural aggravation ($p > 0.05$) and new seizure types ($p < 0.05$) even though 67.9% of CLB co-medicated patients were reduced in CLB in the initial CBD treatment phase.

TABLE 2 Adverse effects of cannabidiol (CBD) in the total patient group, in the clobazam (CLB) group and non-CLB group, and causes of CBD termination in the 27 patients discontinued in cannabidiol treatment. The values are % (n).

	Total patient group (N_{tot} = 78)	CLB group (N_c = 28)	Non-CLB group (N_n = 50)	Discontinued CBD (N_d = 27)
Adverse effects of CBD				
None	21.8 (17)	17.9 (5)	24.0 (12)	
Fatigue	46.2 (36)	60.7 (17)	38.0 (19)	
Increased seizure activity	38.5 (30)	32.1 (9)	42.0 (21)	
Decreased appetite	14.1 (11)	14.3 (4)	14.0 (7)	
Diarrhoea	12.8 (10)	14.3 (4)	12.0 (6)	
Behavioural aggravation	11.5 (9)	21.4 (6)	6.0 (3)	
Nausea/vomiting	9.0 (7)	0 (0)[b, *]	14.0 (7)[b, *]	
Unsteadiness	7.7 (6)	14.3 (4)	4.0 (2)	
New seizure type[a]	3.8 (3)	10.7 (3)[c, *]	0.0 (0)[c, *]	
Constipation	3.8 (3)	7.1 (2)	2.0 (1)	
Rash	2.6 (2)	0 (0)	4.0 (2)	
Headache	1.3 (1)	0 (0)	2.0 (1)	
Causes of CBD termination[d]				
No effect on seizure activity				51.9 (14)
Worsening of seizure activity or status epilepticus				37.0 (10)
Other adverse effects than increased seizure activity				33.3 (9)
Planned fenfluramine medication				7.4 (2)
Death[e]				7.4 (2)
Planned epilepsy surgery				3.7 (1)

*) $p < 0.05$.
a) Atonic, atonic-myoclonic, and undefined.
b) Comparison between nausea/vomiting in CLB- and non-CLB group.
c) Comparison between new seizure type in CLB- and non-CLB group.
d) > 1 cause can be registered for each patient.
e) No deaths were related to CBD.

Table 2 has been updated on May 6th 2021 due to an error.

Cannabidiol termination

By one-year follow-up, 38.8% of patients had discontinued CBD and by two-year follow-up, this was 66.7%. Median treatment time for discontinued patients was 9.1 months (0.7-21.3 months). In most cases, discontinuation of CBD was a mutual decision between the physician and the guardian due to either lack of effect or unacceptable AEs. See Table 2 for causes of CBD termination.

For paraclinical changes, EEG changes and effect on mental state and sleep, **see Supplementary material** https://ugeskriftet.dk/files/a07200527_supplementary.pdf.

DISCUSSION

In the RCTs [1-3] on CBD treatment in DS and LGS, 36-44% of patients had a ≥ 50% seizure reduction over a 12-week steady CBD dosage treatment period compared with 14-27% in the placebo groups. This study found that 31.4% of patients had a ≥ 50% seizure reduction in the total SFR group (Figure 1A, three months) with 70.0% in the DS/LGS SFR group but only 22.0% in the non-DS/LGS SFR group at three months (Figure 2C, three months); hence, this was not higher than in some of the placebo groups in the RCTs. This makes individual close evaluation of effect necessary in case of continued use of CBD in the non-DS/LGS group when giving this severely afflicted group the possibility of CBD as a future treatment choice. Patients in the non-DS/LGS group having some degree of seizure reduction, viz. 65.9% after three months and 41.7% after 12 months. This is also an important effect to consider in this patient group, where other treatment options are exhausted.

Patients in this study were among the most treatment refractory at the Paediatric Department, Filadelfia Epilepsy Hospital. The effect of CBD on seizure reduction could possibly be increased if CBD were to be initiated earlier, but both the effect and cost of CBD in comparison to other AEDs need to be considered when making a treatment choice in patients with severe refractory epilepsy.

In this study in general, the effect on seizures was higher in CLB co-medicated patients than in non-CLB patients, though this difference was only significant in the CLB non-SFR group compared with the non-CLB non-SFR group at three months (Figure 2B). This might be because 67.9% of patients on CLB co-medication were reduced in CLB dosage during the initial phase of CBD treatment to ameliorate AEs, especially fatigue. CBD has shown a 1.6-fold increase in the plasma CLB level and a 3.4-5.0-fold increase in plasma nCLB, though the pharmacokinetic variability of CLB is extensive [10-12]. Part of the effect of CBD on seizures in CLB co-medicated patients is mediated by this increase in nCLB, though CBD has an independent antiseizure effect [11, 13, 14]. Interactions between CBD and other AEDs are also known [15]. Alanine transaminase (ALT) increase in CBD treatment is well known especially in valproate co-medication [15-17], as seen in this study (**see Supplementary material** https://ugeskriftet.dk/files/a07200527_supplementary.pdf). This common increase in TDM and ALT makes frequent blood tests necessary, especially after CBD dosage increment.

One challenge with respect to study design was patients without a BL registration, where the first treatment month registration was used as BL, which is likely to underestimate the effect of seizure reduction, which was not the case though (**see Supplementary figure** https://ugeskriftet.dk/files/a07200527_supplementary.pdf). In patients without SFR, the guardians were at risk of a subjective evaluation, and hence prone to report bias [18]. Long-term SFR carries a risk of seizure underreporting causing an overestimation of seizure reduction. Furthermore, changes in concomitant epilepsy treatment make evaluation of CBD effect more difficult and prone to bias. In this clinical setting, this study design was the best option to evaluate the long-term effects of off-label CBD treatment.

CONCLUSIONS

In this study, off-label CBD treatment of severe refractory epilepsy in a variety of epilepsy diagnoses in children and young adults with predominantly motor seizures showed a ≥ 50% seizure reduction in 31.4% of patients after three months and in 28.1% after 12 months. If co-medicated with CLB, 40.0% had a ≥ 50% seizure reduction after three months and 35.7% after 12 months. The effect was considerably lower in patients without SFR with no effect at 18 months. Epidyolex is now an authorised treatment option of epilepsy in addition to CLB in DS and LGS in patients older than two years of age. This study opens to continued use of CBD as an off-label treatment option in children and young adults with severe refractory epilepsy with motor seizures in a variety of epilepsies other than DS and LGS. SFR with BL is important to evaluate any effect on seizure reduction every third month in

order to taper off CBD in case the effect is lacking. Preferably, CBD treatment should be combined with CLB co-medication though this increases the risk of fatigue, behavioural aggravation and new seizure types. Frequent blood tests with TDM (including nCLB, if appropriate), full blood count, kidney and liver function tests are recommended. Out-patient CBD initiation may be an option, requiring close attention to AEs, recommended blood tests and the need for any CLB reduction. A slower CBD increment plan may be advisable.

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Accepted 11 March 2021

Conflicts of interest none. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2021;68(5):A07200527

Correction: Tables 1 and 2 and Figure 1 have been updated on May 6th 2021 due to an error.

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