ORIGINAL ARTICLE

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Real-world data on cannabidiol treatment of various epilepsy subtypes: A retrospective, multicenter study

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Abstract

Objective: Cannabidiol (CBD) is approved for treatment of Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), and tuberous sclerosis complex (TSC). Several studies suggest antiseizure effects also beyond these three epilepsy syndromes.

Methods: In a retrospective multicenter study, we analyzed the efficacy and tolerability of CBD in patients with epilepsy at 16 epilepsy centers.

Results: The study cohort comprised 311 patients with epilepsy with a median age of 11.3 (0-72) years (235 children and adolescents, 76 adults). Therapy with CBD was off-label in 91.3% of cases due to age, epilepsy subtype, lack of adjunct therapy with clobazam, and/or higher dose applied. CBD titration regimens were slower than recommended, with good tolerability of higher doses particularly in children. Of all patients, 36.9% experienced a reduction in seizure frequency of >50%, independent of their epilepsy subtype or clobazam co-medication. The median observation period was 15.8 months. About one third of all patients discontinued therapy within the observation period due to adverse effects or lack of efficacy. Adverse effects were reported frequently (46.9%).

Significance: Our study highlights that CBD has an antiseizure effect comparable to other antiseizure medications with a positive safety profile independent of the epilepsy subtype. Comedication with clobazam was not associated with a better outcome. Higher doses to achieve seizure frequency reduction were safe, particularly in children. These findings call for further trials for an extended approval of CBD for other epilepsy subtypes and for children <2 years of age.

KEYWORDS
cannabidiol, clobazam, drug-resistant seizures, DS, epilepsy, LGS, TSC

1 | INTRODUCTION

The interest in the medical use of plant-based cannabidiol (CBD), a nonpsychotropic phytocannabinoid, is high given its multiple reported effects.[1–4] Several studies have highlighted its antiseizure effect in children with drug-resistant epilepsy (DRE).[5–9] Phase III studies of CBD reported promising effects on seizure frequency and associated problems in Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS) and tuberous sclerosis complex (TSC).[10–16] The latter findings led to an approval for these indications.

Epidyolex is approved by EMA up to a dose of 20 mg/kg/d for individuals >2 years with LGS or DS, and with a higher maximum dose of 25 mg/kg/d in those with

Key points

- CBD has an antiseizure effect comparable to other antiseizure medications with a positive safety profile independent of the epilepsy subtype.

- Comedication to CBD with clobazam is not associated with a better outcome.

- Higher CBD doses than recommended in studies leading to approval to achieve seizure frequency reduction were safe, particularly in children.

TSC.[10–16] Due to FDA Epidyolex is approved for those epilepsy subtypes over an age of 1 year and above. In Europe, the approval for LGS and DS requires an adjunct treatment with clobazam, while the adjunctive treatment with clobazam is not mandatory in other countries such as the USA, since an independent benefit of CBD has been proven.[17–20] Overall, CBD seems to have a good safety profile.[3,5,21]

Given the need for novel treatment options particularly in DRE, we hypothesized that CBD could be a promising ASM and had been offered "off label" in individuals with epilepsy subtypes beyond LGS, DS, and TSC. Here, we aimed to collect real-world data on the application, dosing, adverse effect profile, and efficacy of CBD in more than 300 children and adults with various epilepsy subtypes.

2 | PATIENTS AND METHODS

We conducted a retrospective, multicenter study at 16 epilepsy centers based on medical records of 311 patients with epilepsy who were treated with CBD as antiseizure medication in Germany between December 2015 and December 2021. Epidyolex® was used in 220 (70.7%) patients, and the CBD formulation standardized in Germany (Neues Rezeptur Formularium 22.10, NRF)[22] containing 100 mg/mL CBD dissolved in medium chain triglycerides in 91 (29.3%) subjects.

NRF 22.10 is available in Germany as a nonprescription drug available in pharmacies and was used synonymously with Epidyolex prior to approval. We have decided to include both NRF 22.10 and Epidyolex as they contain the same active ingredient concentration of highly purified CBD derived from *Cannabis sativa* plant and almost the same composition of additives (medium-chain triglycerides, with an additional low ethanol content in Epidyolex).

We included all patients with epilepsy who received CBD as an ASM and could be identified in patient records of the participating study centers. Six patients, who were treated with drugs containing CBD other than oral Epidyolex® or NRF, were excluded from the analysis. The retrospective analysis of epilepsy patient data was approved by the local ethic committee (approval no. EA2/084/18). The need for informed consent was waived.

We extracted seizure- and treatment-specific data from electronic and paper-based medical records using a standardized data collection sheet. Patient information and information on epilepsy as well as treatment and outcome were documented in the clinical information system by specialists at the respective epilepsy centers. Seizure outcome was assessed by the specialist treating the patients and was based on patient history, seizure diaries, and/or parental declaration in minors. Seizure outcome was assessed at the last follow up and divided into the categories: seizure freedom, seizure reduction >50%, seizure reduction <50%, and no effect/worsening. Missing data were marked in the dataset, but core data were available in all patients, so no patient had to be excluded.

Data were stored in REDCap (https://www.project-redcap.org). Statistical analysis was conducted with IBM SPSS Statistics Version 25 program and specific tests are mentioned in the result section. Test results with $P < 0.05$ were considered statistically significant. Figures were generated with the help of GraphPad Prism version 9.3.1 (GraphPad Software, San Diego, CA, USA).

3 | RESULTS

Our cohort comprised 311 patients (235 children, 76 adults) with epilepsy who were treated with CBD (Table 1). In our cohort, the majority of patients (66.2%) had epilepsy syndromes or etiologies other than LGS (n = 65, 20.9%), DS (n = 28, 9.0%), and TSC (n = 12, 3.9%). The etiology of epilepsy was predominantly genetic (n = 111, 35.7%; eg, DS, LGS, Angelman syndrome, Rett syndrome) or structural (n = 105, 33.8%; eg, hypoxic encephalopathy, structural defects secondary to infection, FCD, gyration disorder), followed by an unknown (n = 58, 18.6%) or genetic & structural (n = 37, 11.9%; eg, TSC, lissencephaly) etiology (Table 1, Tables S1 and S2). Prior to the introduction of CBD, 19 patients had undergone epilepsy surgery including hemispherotomy (n = 8), selective amygdalo-hippocampectomy (n = 3), temporoparietal lobe disconnection (n = 2), and lobectomy (n = 2).

3.1 | Concomitant antiseizure medication

Before CBD was added, patients had been treated with a median total number of five ASM (range 0-16), and 74.9% (n = 233) of all patients were drug resistant (Tables 1 and 2). Drug resistance was defined as failure of seizure control through two tolerated, appropriately chosen and dosed ASM.[23] The median number of ASM given concomitantly with CBD was 3 (range 0-6). Eleven patients (3.5%) received CBD as monotherapy. 46.3% of the patients received clobazam. Further frequent comedications included valproate (43.1%), lamotrigine (25.4%), levetiracetam (15.8%), brivaracetam (14.8%), and lacosamide (14.5%).

TABLE 1 Overview of cohort and CBD treatment specification.

	Children (n = 235)	Adults (n = 76)	Total (n = 311)
Sex			
Female	103 (44.6%)	35 (46.1%)	138 (44.4%)
Male	128 (55.4%)	41 (53.9%)	169 (54.3%)
Unknown	4 (1.7%)	0	4 (1.3%)
Age years, median ± SD (range)	9 ± 4.5 (0.2-17.9)	29.4 ± 10.8 (18-72)	11.3 ± 11.3 (0.2-72)
Etiology			
Structural	77 (32.8%)	28 (36.8%)	105 (33.8%)
Genetic	90 (38.3%)	21 (27.6%)	111 (35.7%)
Structural + genetic	34 (14.5%)	3 (3.9%)	37 (11.9%)
Unknown	34 (14.5%)	24 (31.6%)	58 (18.6%)
Approved indications			
Lennox-Gastaut syndrome	44 (18.7%)	21 (27.6%)	65 (20.9%)
Dravet syndrome	20 (8.5%)	8 (10.5%)	28 (9.0%)
Tuberous sclerosis	12 (3.9%)	0	12 (3.9%)
Seizure type			
Focal onset	153 (65.1%)	61 (80.2%)	214 (68.8%)
Motor	133 (56.6%)	47 (61.8%)	180 (57.9%)
Nonmotor	70 (29.8%)	34 (44.7%)	104 (33.4%)
Focal to bilateral tonic-clonic	41 (17.4%)	29 (38.2%)	70 (22.5%)
Generalized onset	183 (77.8%)	51 (67.1%)	234(59.2%)
Motor	168 (71,5%)	50 (65.8%)	218 (70.0%)
Nonmotor	70 (29.8%)	19 (25%)	89 (28.6%)
Unknown onset	11 (4.7%)	0 (0%)	11 (3.5%)
No. of medications			
Previous ASM	5 ± 3.4 (0-16)	8 ± 2.7 (1-13)	6 ± 3.4 (0-16)
Comedication ASM	3 ± 1.1 (0-6)	3 ± 1.1 (0-5)	3 ± 1.1 (0-6)
Lifetime ASM	8 ± 3.9 (1-19)	10 ± 4.2 (1-17)	8 ± 4.0 (1-19)
CBD dosage in mg/kg/d, median ± SD (range)			
start dose ± SD	3.3 ± 2.2 (0.08-20)	2.8 ± 1.5 (0.77-5.7)	3.2 ± 2.0 (0.08-20.0)
Titration *per week*	2.8 ± 1.6 (0.08-10.6)	2.66 ± 1.2 (0.62-5.7)	2.8 ± 1.6 (0.08-10.6)
End dose± SD	19.0 ± 7.8 (2.56-45)	13.3 ± 6.15 (2.5-32)	17.8 ± 7.7 (2.5-45)
Follow-up			
No. of treatments ended Duration	68 (28.9%) 5.5 ± 8.4 m (7 d to 41.7 m)	27 (35.5%) 7.0 ± 6.4 m (3 d to 24.1 m)	95 (30.5%) 6.2 ± 7.8 m (3 d to 41.7 m)
Reason to end			
No effect	42 (17.9%)	19 (25%)	61 (19.6%)
Side effects	21 (8.9%)	8 (10.5%)	29 (9.3%)
Other	11 (4.6%)	4 (5.3%)	15 (4.8%)
No. of ongoing treatments Duration	167 (71.1%) 21.7 ± 15.7 m (17 d to 5.9 y)	49 (64.5%) 20.3 ± 16.2 m (8 d to 5.59 y)	216 (69.5%) 21.4 ± 15.8 m (8 d to 5.9 y)

(Continues)

TABLE 1 (Continued)

	Children (n = 235)	Adults (n = 76)	Total (n = 311)
Effect on seizures			
Seizure freedom	17 (7.2%)	3 (3.9%)	20 (6.4%)
Reduction >50%	73 (31.1%)	22 (27.9%)	95 (30.5%)
Reduction <50%	72 (30.6%)	25 (32.9%)	97 (31.2%)
No change	56 (23.8%)	16 (21.1%)	72 (23.2%)
Increased frequency	17 (7.2%)	10 (13.2%)	27 (8.7%)
Effect reduction >3 months			
Yes	39 (16.6%)	6 (7.9%)	45 (14.5%)
No	63 (26.8%)	24 (31.6%)	87 (28.0%)
n.a.[a]	133 (56.6%)	46 (60.5%)	179 (57.6%)
Side effects	107 (45.5%)	39 (51.3%)	146 (46.9%)
Sleepiness	51 (21.7%)	24 (31.6%)	75 (24.1%)
Gastrointestinal symptoms	59 (25.1%)	19 (25.0%)	78 (25.1%)
Psychiatric symptoms	15 (6.4%)	4 (5.3%)	19 (6.1%)
Liver enzyme increase	3 (1.3%)	2 (2.6%)	5 (1.6%)
Muscle weakness	5 (2.1%)	0 (0.0%)	5 (1.6%)
Other effects	3[c] (1.3%)	3[b] (3.9%)	6 (1.9%)
Positive effects			
Improved mood	76 (32.3%)	20 (26.3%)	96 (30.9%)
Improved night sleep	63 (26.8%)	12 (15.8%)	75 (24.1%)
Improved development	37 (15.7%)	2 (2.6%)	39 (12.5%)
Increase in appetite	32 (13.6%)	3 (3.9%)	35 (11.3%)
Reduction of spasticity	22/58 (37.9%)	2/11 (18.2%)	24/69 (34.8%)

[a]Patients with treatment less than 3 month, no prior effect on seizures, assessment not done.

[b]1x dizziness, 1x trembling, 1x increased bronchial secretion.

[c]1x dizziness, 1x trembling, 1x respiratory insufficiency, 1x urine retention.

3.2 | CBD titration

CBD was started at a median age of 11.3 years (range 2 months to 72 years, IQR 7.25-17.83). The median starting dose was 3.2 mg/kg/d (range 0.08-20 mg/kg/d, IQR 2.1-5.0) and did not differ significantly between children (median 3.3 mg/kg/d, range 0.08-20 mg/d) and adults (median 2.8 mg/kg/d, range 0.77-5.7 mg/d) (Figure 1A, Table 1). Up-titration was performed with a median of 2.8 mg/kg per week (range 0.08-10.6, IQR 1.8-4, Figure 1A, Table 1). The median end dose was 17.8 mg/kg/d (range 2.5-45, IQR 11.7-21.93) and was significantly higher in children (median 19.0 mg/kg/d, max. 45.0, Kruskal-Wallis test, $P < 0.0001$) compared to adults (13.3 mg/kg/d, max. 32.0; Figure 1A, Table 1).

3.3 | Effects of CBD treatment

The median follow-up of all patients was 15.8 months (3 days to 5.9 years, IQR 6.9 month to 2.2 years; Table 1). Approximately one-third (n = 95, 30.5%) of the patients terminated therapy within the observation period. The median duration of treatment in this group was 6.2 months (range 3 days to 41.7 months). Reasons for discontinuation were lack of sufficient therapeutic efficacy (n = 61, 19.6%), adverse effects (n = 29, 9.3%), and other causes such as nonadherence, lack of reimbursement by the health insurance, pregnancy, and nontherapy-related death. 18 patients of 311 patients discontinued the treatment before 3 months of treatment due to lack of effect or increased seizure frequency (n = 6), to side effects (n = 10)

TABLE 2 Rates of seizure freedom dependent on successive ASM regimens including CBD.

No. of ASMs tried including CBD	Total no. (%) of patients (n = 311)	Seizure freedom (n = 20)		Seizure reduction >50%, (n = 95)		Seizure freedom + Seizure reduction >50% (n = 115)	
		No. (%) of pat. Within group	% of pat. Of total cohort	No. (%) of pat. Within group	% of pat. Of total cohort	No. (%) of pat. Within group	% of pat. Of total cohort
First	2 (0.6%)	1 (5.0%)	0.6%	0	0	1 (0.7%)	0.3%
Second	26 (8.4%)	3 (15.0%)	1%	4 (4.2%)	1.3%	7 (6.1%)	2.3%
Third	22 (7.1%)	2 (10.0%)	0.6%	6 (6.3%)	1.9%	8 (7.0%)	2.6%
Fourth	32 (10.3%)	1 (5.0%)	0.3%	14 (14.8%)	4.5%	15 (13.0%)	4.8%
Fifth	25 (8.0%)	2 (10.0%)	0.6%	7 (7.4%)	2.3%	9 (7.8%)	2.9%
Sixth	20 (6.4%)	2 (10.0%)	0.6%	5 (5.3%)	1.6%	7 (6.1%)	2.3%
Seventh	35 (11.3%)	1 (5.0%)	0.3%	10 (10.5%)	3.2%	11 (9.6%)	3.5%
Eighth	24 (7.7%)	0	-	7 (7.4%)	2.3%	7 (6.1%)	2.3%
Ninth	21 (8.8%)	3 (15.0%)	1%	6 (6.3%)	1.9%	9 (7.8%)	2.8%
Tenth	18 (5.8%)	3 (15.0%)	0.6%	5 (5.3%)	1.6%	8 (7.0%)	2.6%
Eleventh	17 (5.5%)	1 (5.0%)	0.3%	7 (7.4%)	2.3%	8 (7.0%)	2.6%
Twelfth	9 (2.9%)	0	-	2 (2.1%)	0.6%	2 (1.7%)	0.6%
Thirteenth	7 (2.3%)	0	-	2 (2.1%)	0.6%	2 (1.7%)	0.6%
Fourteenth	5 (1.6%)	0	-	3 (3.2%)	1.0%	3 (2.6%)	0.9%
Fifteenth	3 (0.6%)	0	-	1 (1.1%)	0.3%	1 (0.9%)	0.3%
Sixteenth	1 (0.3%)	0	-	0	-	0	-
Seventeenth	1 (0.3%)	0	-	0	-	0	-
Unknown	43 (13.8%)	1 (5.0%)	0.3%	16 (16.8%)	5.1%	17 (14.8%)	5.5%

(tiredness (n = 5), gastrointestinal side effects (n = 4), psychiatric symptoms (n = 1)), incompliance (n = 1), and not therapy-related death (n = 1).

The median follow-up of the other patients (n = 216, 69.5%) who did not end the treatment was 21.4 months (8 days to 5.9 years; Table 1). In the entire cohort after a median treatment duration of 15.8 months (range 3 days to 5.9 years, IQR 6.9 month to 2.2 years) following CBD introduction seizure frequency was reduced in 192 of 311 patients (61.7%), thereof seizure reduction of >50% was obtained in 95 of 311 patients (30.5%), and seizure-freedom was obtained in a further 20 patients (6.4%). Looking specifically only at the 20 patients who were seizure-free, the observation period was median 21 months (range 3.1 months to 5.7 years). In 23.2% of all patients (n = 72), no change of seizure frequency occurred, and 8.7% (n = 27) showed an increased seizure frequency. Previous treatments of those 20 patients included ASM treatment with levetiracetam (n = 14), oxcarbazepine (n = 10), sultiame (n = 10), topiramate (n = 10), valproic acid (n = 7), lamotrigine (n = 6), ethosuximide (n = 5), lacosamide (n = 5), zonisamide (n = 4), rufinamide (n = 4), vigabatrin

(n = 3), phenobarbital (n = 3), carbamazepine (n = 2), clobazam (n = 2), perampanel (n = 2), phenytoin (n = 2), brivaracetam (n = 1). One patient had undergone hemispherotomy before CBD treatment.

The outcome for patients with LGS, DS, and TSC did not significantly differ from other epilepsy subtypes. Seizure freedom was achieved in 7% in LGS, 5% in DS, and 1.3% in TSC (Table S3).

Significant higher doses (Kruskal-Wallis test, multiple comparison, $P = 0.0003$) were applied in patients with seizure reduction compared to patient with no CBD effect. The CBD effect correlated with the CBD end dose (Kruskal-Wallis test, $P = 0.00014$) (Figure 1B). The CBD effect did not correlate with age at CBD initiation (Kruskal-Wallis test, $P = 0.3904$). Patients receiving clobazam as comedication had no significantly improved effect on seizure frequency reduction compared to patients without clobazam (Chi-square test, $P = 0.5084$; Figure 1C).

To address a potential honeymoon effect of CBD, we assessed a possible reduction of the effect of CBD on seizure frequencies after the first 3 months of CBD treatment
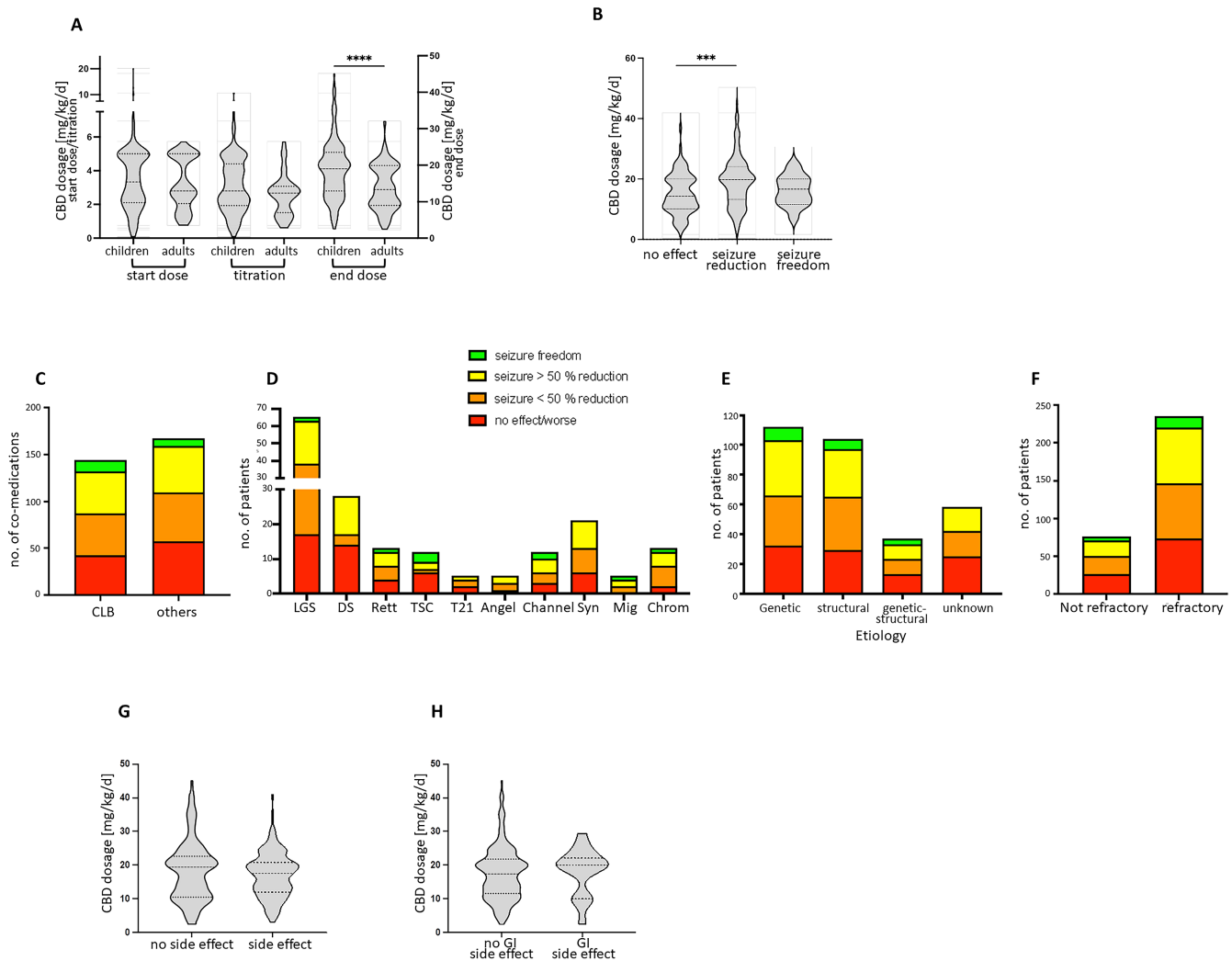
FIGURE 1 A. Violine plot of CBD dosage [mg/kg/d] showing start, titration, and end dose for children and adults. ****Children received a significant (Mann-Whitney test, start dose: $P = 0.5235$ titration: $P = 0.0941$, end dose: $P < 0.0001$) higher end dose than adults. (A, C, H, I) Lines showing median and quartiles. B. Violine plot of CBD dosage in [mg/kg/d| shown for patients with no effect of CBD on seizures, seizure reduction <50% and >50%, and seizure freedom. Lines are showing median and quartiles. ***Significant higher doses were applied in patients with seizure reduction compared to patient with no CBD effect (Kruskal-Wallis test, multiple comparison, $P = 0.0001$, no effect/worse: median: 14.25, IQR: 10-0-20.0; <50% reduction: median: 18.0, IQR: 11.95-21.85; >50% reduction: median 20.0, IQR: 15.0-25.0; seizure freedom: median 16.7, IQR 11.58-20.0). C. Boxplot of number of patients treated with a concomitant CLB or other co-medication. (C-F): Colors showing outcome of the effect of CBD on seizures: red = no effect/ more seizures, orange = seizure reduction <50%, yellow = seizure reduction >50%, green = seizure freedom. D. Boxplot of number of patients sorted by genetic syndromes and causes of epilepsies and outcome due to CBD treatment (Chi square test, $P = 0.15$). LGS = Lennox-Gastaut Syndrome, DS = Dravet Syndrome, Rett = Rett syndrome, TSC = Tuberous Sklerosis Complex, T21 = trisomy 21, Angel = Angelman syndrome, Channel = channelopathies, Syn = Synapsis, Mig = migration disorders, Chrom = chromosomal abnormalities. E. Boxplot of number of patients sorted by etiology of their epilepsies and outcome due to CBD treatment (Chi square test, $P = 0.36$). F. Boxplot of number of patients sorted by refractory or nonrefractory epilepsy epilepsies and outcome due to CBD treatment (Chi square test, $P = 0.93$). G. In our cohort CBD dosage [mg/kg/d| had no effect on the presence of side effects in general (Mann-Whitney test, $P = 0.4466$) or H. gastrointestinal (GI) side effects (Mann-Whitney test, $P = 0.5097$).

(Table 1). Excluding patients without a positive effect on seizures in the first 3 months of treatment and those with a treatment duration under 3 months (n = 102), the initial positive effect decreased in 21.5% (45/209) and remained stable in 41.6% (87/209) of patients. In 36.8% (77/209) these data were not available.

The effect of CBD on seizures did not differ significantly between individuals with the epilepsy subtypes approved for CBD treatment (LGS, DS, TSC) and those with other epilepsy subtypes (Figure 1D). None of the patients with DS became seizure-free. The outcome of the various patient groups depending on the etiology and

drug resistance of their epilepsy subtype is illustrated in Figure 1D-F.

3.4 | Adverse effects of CBD treatment

Adverse effects were reported in almost half of the patients (n = 146, 46.9%) and overall did not correlate with the CBD dosage (Table 1; Figure 1G). These included particularly reduced vigilance and tiredness in 75 patients (24.1%) as well as nondose-dependent gastrointestinal adverse effects in 78 patients (25.1%) (Figure 1H), including diarrhea in 38 cases. Moreover, 19 patients (6.1%) reported psychiatric symptoms such as aggressiveness, panic attacks, and psychotic symptoms. In five cases increased liver enzymes were reported. Four of these received valproate as comedication out of a total of 130 patients receiving valproate comedication (88 with available liver values). Adverse effects resulting in treatment interruption occurred in 29 of all 311 patients (9.3%) and included gastrointestinal adverse effects such as diarrhea (n = 12, 3.9%), sleepiness (n = 6, 1.9%), psychiatric symptoms (n = 6, 1.9%), muscle weakness (n = 2, 0.6%), and dizziness (n = 1, 0.3%).

3.5 | Positive side effects

Perceived positive effects of the CBD therapy were improved mood (n = 96, 30.9%), improved night sleep (n = 75, 24.1%), improved development and concentration (n = 39, 12.5%), and increase in appetite (n = 35, 11.3%). Spasticity was reduced in 24 of 69 patients (34.8%) (Table 1).

4 | DISCUSSION

We report the dosing, efficacy, and tolerability of CBD treatment in a large cohort of 311 children and adolescents with various epilepsy syndromes and etiologies in a retrospective multicenter study. We provide real-world data including off-label applications. Our cohort included 75.6% patients with DRE. We provide information on the real-world CBD dosing regimen. Moreover, we show that the efficacy of treatment with CBD in epilepsy does not differ between individuals with LGS, DS, and TSC and those with other epilepsy subtypes. Due to the results of our study CBD seems not to offer a disease targeted effect relating to seizure generation or pathology of DS, LGS, or TSC. Therapy with CBD was off-label in most cases (91.3%) due to age under 2 years (n = 28), epilepsy subtype (n = 206), lack of adjunct therapy with clobazam (n = 167), and/or higher dose applied than approved (n = 93).

The EMA dosing recommendation for CBD specifies a starting dose of 5 mg/kg/d in two doses with a weekly up-titration by 5 mg/kg/d to a maximum dose of 20 mg/kg/d for LGS and DS and to 25 mg/kg/d for TSC. The starting dose of CBD in the present cohort was lower with a median 3.2 mg/kg/d, and up-titration was also performed less rapid with steps of a median of 2.8 mg/kg per week. While the median end dose applied to individuals in our study was as recommended by the producer (median 19.0 mg/kg/d in children and 13.3 mg/kg/d in adults), it was significantly lower in adults. The maximum dose applied was higher in children (max. 45 mg/kg/d) than in adults (max. 32 mg/kg/d). The dosing in children <2 years of age was similarly performed.

Treatment of all individuals with various epilepsy subtypes resulted in seizure freedom in 6.4%, seizure reduction >50% in 30.5%, and seizure reduction <50% in 31.2%. The effect was independent of the coadministration of clobazam, supporting that an introduction of clobazam to meet in-label treatment restraints[24] may not be maintained.

The use of CBD as the first administered ASM appears to be less effective compared to other ASMs, we observed a lower rate of seizure freedom in our cohort than published by Chen et al, although the number of first-line therapies in our cohort is little[25] (Table 2). The efficacy as a third or fourth drug corresponds to that from previous studies.[25–27] The fact that CBD, as a relatively new ASM, has already been used in non-DRE (78 patients, 25.1%) in our cohort might reflect the high expectations regarding its efficacy.

Seizure freedom or seizure frequency reduction >50% was seen in 40.8% of patients with LGS, DS, or TSC and in 36.9% of those with non-LGS, non-DS, and non-TSC epilepsy. No patients with DS attained seizure freedom. Our retrospective data show similar effectiveness of CBD in in-label epilepsy types compared to the effectiveness shown in randomized and controlled studies, leading to approval in LGS, DS, and TSC (Table S3).[10–13,16,28] This did not differ between those individuals with LGS, DS, and TSC receiving CLB compared to those not receiving that comedication. This intriguing finding could be due to selection bias with highly DRE patients included in the present study versus the strict selection criteria of the previous studies, which makes reproducibility in real-word data studies challenging to achieve.[10,13,14] Thus, we cannot confirm a unique seizure reduction for LGS, DS, and TSC in our study, but rather support the effectiveness in a larger spectrum of epilepsy subtypes.[29,30]

A honeymoon effect is known for many ASM,[25,31,32] and we here demonstrate that this is also the case for CBD. One-fifth of patients who had reported seizure freedom or reduced seizure frequency (> or <50%) in the first 3 months showed reduced efficacy after 3 months, indicating a honeymoon effect in CBD.[33] Another recently published

open-label study reported that about one-third of children and adults with epilepsy subtypes showed some tolerance to CBD.[20] In a study by Thiele et al.[14] that led to the approval of CBD, no evidence for the tolerance of CBD could be found; a possible honeymoon effect was first assessed after one year of treatment with CBD. Further studies are needed to address a potential honeymoon effect.

In addition to the effect on seizures, we observed effects on soft signs in 42.1% of all patients similar to findings in previous studies.[4,8] These effects included improved mood, night sleep, development, and appetite as well as reduction of preexisting spasticity. We feel this to be a potent strength of CBD, although not jet sufficiently defined, and suggest focusing on those soft signs on shorter time intervals in further investigations. Furthermore, the relatively high placebo effect, which was already evident in previous studies, must be mentioned.[20,34] In addition to a reduction in seizure frequency with placebo use in the RCTs, there were also positive effects on soft markers.[11,14,17,21]

Overall, the drug tolerability was good with known adverse effects in 146 patients (46.9%) that were, however, not severe and well-controllable.[10,11,15,16,29,35] The profile of adverse effects did not differ between in-label and off-label treatment (Table S3). The most prominent adverse effects that occurred in about a quarter of the patients were gastrointestinal adverse effects and reduced vigilance. Increased sleepiness was observed particularly in those cases concomitantly treated with clobazam (32.6%, 47/144) versus those without clobazam (16.7%, 28/167). Less frequently, psychiatric symptoms or elevation of liver enzymes occurred. Given the low number of cases with liver toxicity when CBD was added to valproic acid in our study, we cannot infer valproic acid as a clear risk factor but suggest close monitoring as part of the protocol.[10,11,13,28] Overall, adverse effects led to a discontinuation of the therapy in only 9.3% (n = 29). The most frequent cause was diarrhea, which has been previously reported and linked in some cases to sesame oil allergy.[36] Several patients or caretakers rated a softer stool as positive in individuals with frequent constipation. Neither diarrhea nor the other adverse effects in our study were dependent on the CBD dose, in contrast to previous studies.[10–12] Our results support the overall good safety profile with tolerable adverse effects of CBD in a real-world data study, in line with previous randomized controlled trials.[11,13,36,37]

However, limitations of our study were a retrospective design with missing data, heterozygous documentation between the centers, possible confounders such as prior medication, diets, epilepsy surgery. Additionally, the cohort was heterogeneous in age, seizure type, and CBD titration plan.

In summary, we highlight an overall seizure freedom rate of CBD comparable to that of many other ASMs in DRE[25] with a positive safety profile. We show that comedication with clobazam was not associated with a better outcome and that higher end doses were safely applied, particularly in children, to achieve reduction of seizure frequency. This applies to children and adults with various epilepsy subtypes. Our data, therefore, call for further trials to aim for an extended approval of CBD for other epilepsy subtypes and for children <2 years of age.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

AMK, FK, CP, KAK contributed to the conception and design of the study. FK, LLB; TB, AB, IB,CMB, JF, CH, NAH, MH, MH, CJ, GJK, GK, HL, KLM, FP, MP, SSB, JS, ASB, DS, BJS, AS, SS, HDV, CW, JW, BW, CP, KAK, AMK contributed to acquisition of data. FK organized the database, FK and LLB analyzed the data. FK wrote the first draft of the manuscript, FK and LLB created tables and figures. All authors discussed the results, revised the first draft, and contributed to the final manuscript.

CONFLICT OF INTEREST STATEMENT

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.