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Retrospective chart review study of use of cannabidiol (CBD) independent of concomitant clobazam use in patients with Lennox-Gastaut syndrome or Dravet syndrome

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ABSTRACT

Purpose: This retrospective chart review study (GWEP20052) evaluated plant-derived highly purified cannabidiol (CBD; Epidyolex®; 100 mg/mL oral solution) use without clobazam as add-on therapy in patients aged ≥2 years with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) enrolled in a European Early Access Program.
Methods: Data were extracted from patient charts covering a period starting 3 months before CBD treatment and concluding after 12 months of CBD treatment, or sooner if a patient discontinued CBD or started clobazam.
Results: Of 114 enrolled patients, data were available for 107 (92 LGS, 15 DS) who received CBD without clobazam for ≥3 months. Mean age: 14.5 (LGS) and 10.5 (DS) years; female: 44% (LGS) and 67% (DS). Mean time-averaged CBD dose: 13.54 (LGS) and 11.56 (DS) mg/kg/day. Median change from baseline in seizure frequency per 28 days over 3-month intervals varied from −6.2% to −20.9% for LGS and 0% to −16.7% for DS. Achievement of ≥50% reduction in drop (LGS) or convulsive (DS) seizures at 3 and 12 months: LGS, 19% (n = 69) and 30% (n = 53); DS, 21% (n = 14) and 13% (n = 8). Retention on CBD without clobazam (enrolled set): 94%, 80%, 69%, and 63% at 3, 6, 9, and 12 months. Adverse event (AE) incidence was 31%, most commonly somnolence, seizure, diarrhea, and decreased appetite. Two patients discontinued CBD owing to AEs, and four patients with LGS experienced elevated liver enzymes.

Abbreviations: AE, adverse event; AED, antiepileptic drug; ALT, alanine transaminase; ASM, antiseizure medication; AST, aspartate transaminase; CBD, cannabidiol; DDI, drug-drug interaction; DS, Dravet syndrome; EAP, Early Access Program; EMA, European Medicines Agency; EU, European Union; GGT, gamma-glutamyltransferase; IEC, Independent Ethics Committee; LGS, Lennox-Gastaut syndrome; NHS, National Health Service; Q1, first quartile; Q3, third quartile; RCT, randomized controlled trial; SAE, serious adverse event; SD, standard deviation; SE, standard error; TSC, tuberous sclerosis complex; UK, United Kingdom.

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Conclusion: Results support favorable effectiveness and retention of CBD without concomitant clobazam for up to 12 months in clinical practice.

1. Introduction

Highly purified add-on cannabidiol (CBD) is approved as Epidiolex® in the USA for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients ≥1 year of age [1] and as Epidyolex® in the UK/EU in conjunction with clobazam for LGS and DS in patients ≥2 years of age [2]. It is additionally approved for TSC in patients ≥2 years of age in the UK/EU without clobazam [2]. The objective of this retrospective chart review study was to evaluate the seizure reduction, retention, and safety profile of CBD treatment without concomitant clobazam in patients with LGS or DS.

LGS and DS are rare and severe developmental and epileptic encephalopathies with onset in infancy or early childhood and that persist into adulthood [3–5]. LGS is characterized by multiple seizure types (including tonic, atonic, and atypical absence seizures), abundant slow spike-wave complexes in interictal electroencephalogram, and intellectual disability [6–8]. DS is associated with early-onset hemi-clonic, convulsive seizures, often triggered by fever, which may be prolonged or result in status epilepticus [9,10]. Most cases are caused by pathogenic variants in the sodium channel gene *SCN1A*, but several other genes have also been implicated [11]. Treatment of both syndromes is challenging owing to drug resistance, multiple seizure types, comorbidities, and balancing adverse events (AEs) [7,9]. Available treatments are unlikely to lead to seizure freedom, and the goal is to improve seizure control, learning, behavior, and quality of life [9,12].

Add-on CBD has demonstrated clinically significant reduction in drop seizures (LGS) and convulsive seizures (DS) versus placebo with an acceptable safety profile in four phase 3 randomized controlled trials (RCTs; two trials in LGS and two trials in DS) [13–16]. The aim of these trials was to evaluate CBD as an add-on treatment to the patient's current antiseizure medication (ASM), commonly referred to as antiepileptic drugs (AEDs), and they included patients both on (LGS, 49%; DS, 64%) and off clobazam [13–16]. The combination of CBD and clobazam has generated interest because a drug-drug interaction (DDI) exists between CBD and clobazam that, in some cases, leads to increased exposure of the major active metabolites of both compounds [17–20]. However, the phase 3 RCTs were powered to demonstrate efficacy of CBD alongside any concomitant ASMs, not specifically clobazam. Subsequently, following review of subgroup analyses of patients on and off clobazam, the European Medicines Agency (EMA) concluded that an independent effect of CBD could not be demonstrated for the primary endpoint and approved its use in association with clobazam [21].

Following the EMA decision, meta-analysis of the phase 3 data was conducted to evaluate a CBD effect independent of clobazam. Owing to the limited numbers of patients in the individual RCTs in the on/off clobazam groups, data were pooled into overall, LGS, or DS populations [22,23]. Interestingly, these data indicated that add-on CBD reduces seizures both with and without clobazam. However, somnolence and sedation may occur more frequently in patients taking concomitant clobazam [22,23]. These analyses provide the best current evidence of a CBD effect without concomitant clobazam.

Before EMA approval, an Early Access Program (EAP) was initiated to provide access to CBD for patients with an urgent need for treatment; concomitant administration with clobazam was not initially required. The EAP serves as an additional data source to investigate CBD use without clobazam. Real-world data from the charts of patients with LGS or DS enrolled in the EAP were collected, and an interim analysis of data collected for the first 46 patients enrolled (through November 15, 2021) was presented at the 2022 European Epilepsy Congress [24]. Here, we present the full analysis of this retrospective chart review study.

2. Methods

2.1. Study design

This phase 4, retrospective chart review study included patients aged ≥2 years with LGS or DS treated with CBD without concomitant clobazam as add-on therapy at EU EAP sites between April 2021 and January 2022. Inclusion criteria required patients to be enrolled in the EU EAP, have available patient chart data for at least 3 months before CBD treatment, and have started treatment with CBD without concomitant clobazam. Any patient charts that did not meet the inclusion criteria were excluded from the study. CBD was administered under the direction of a physician with a recommended starting dose of 5 mg/kg/day administered twice daily for 1 week followed by a maintenance dose of 10 mg/kg/day. The dose of CBD could be increased as required with a recommended maximum of 20 mg/kg/day. Other ASMs and treatments for epilepsy were prescribed at the physician's discretion and by local practice.

2.2. Ethics approval

The study was conducted following the principles of Good Pharmacoepidemiology Practice. The study protocol and other relevant documents were approved by the Independent Ethics Committee (IEC) for each site before study initiation. Signed informed consent that met the requirements of the IEC, Institutional Review Board, and local regulations was obtained from patients or legally authorized representatives.

2.3. Data collection

The study sites used an electronic data capture platform to retrospectively collect selected patient chart data into case report forms. Patient demographic and baseline data (age, sex, and primary diagnosis) were collected, as well as treatments received (CBD dose and tapering, primary reason for discontinuation, and ASMs [including ketogenic diet, vagus nerve stimulation, and rescue medication]), AEs, and clinical laboratory evaluations. The number of drop (LGS) or convulsive (DS) seizures in the first 3 months of treatment was collected as a primary outcome. Drop seizures were defined as an attack or spell (atonic, tonic, or tonic-clonic) involving the entire body, trunk, or head that led or could have led to a fall, injury, slumping in a chair, or the patient hitting their head on a surface; convulsive seizures were defined as tonic-clonic, tonic, clonic, and atonic seizures. These seizure types were chosen as the primary outcome for each indication to match the primary endpoints of the phase 3 RCTs. Patients were not provided with seizure diaries for this study; seizure data were collected retrospectively from patient records taken during unscheduled visits. Data were extracted covering a period starting 3 months before CBD treatment and concluding after 12 months of CBD treatment without concomitant clobazam or after CBD discontinuation, addition of clobazam, or the data extraction date. Study sites were provided with definitions of key data variables, and charts were reviewed in chronological order, beginning with the first patient enrolled in the EAP at each site, to minimize bias due to patient selection, measurement, and missing data.

2.4. Statistical analysis

Data were analyzed using descriptive statistics and included all patients with recorded data. The enroled set was defined as all eligible patients who entered the study, while the full analysis set included patients who received CBD without concomitant clobazam for at least 3

months before data extraction. The full analysis set was used for all analyses of outcome measures, except retention, which used the enrolled set. Baseline values were collected over 3 months before the first dose of CBD without concomitant clobazam. Data were analyzed in 3-month intervals where 1 month was defined as 28 days. Endpoints that covered 3 months such as number of seizures were summarized for the entire interval, and point-in-time endpoints such as CBD retention were summarized on the last day of the interval. Missing data were highlighted throughout to prevent under-reporting or bias. Implausible or invalid data were followed up with the site. Data analyses were based upon the number of patients remaining in the study at each time point.

Primary endpoints focused on outcomes for the first 3 months after the initiation of CBD without concomitant clobazam, including percentage change from baseline in mean drop (LGS) or convulsive (DS) seizures per 28 days; achievement of ≥50%, ≥75%, and 100% seizure reduction; and the number of seizure-free days per 28 days. The same outcomes for 3-month intervals ending at Months 6, 9, and 12 after the first dose (4–6, 7–9, and 10–12 months) were analyzed as secondary endpoints. Additional secondary endpoints included CBD retention (3, 6, 9, and 12 months after starting treatment), AEs, and clinically significant changes in liver function tests or other laboratory results. AEs were classified as serious (SAEs) if they resulted in death, threat to life, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect, or were deemed by the investigator to be serious.

3. Results

3.1. Patient disposition

This study was conducted at 19 study sites across Europe, including seven sites in France, four in Germany, four in Italy, two in Spain, and two in the UK. Of the 114 patients enrolled in the study, 107 received CBD without concomitant clobazam for at least 3 months before data extraction and comprised the full analysis set (Fig. 1). Overall, 64/114 (56%) patients remained on CBD without clobazam for ≥12 months and 49/114 (43%) patients remained on CBD without clobazam for <12 months; one patient had no available clinical data (Fig. 1). Of the 49 patients with <12 months of available data, clobazam was added to CBD treatment in 23 patients, and 16 patients discontinued CBD treatment (12 non-efficacy; 3 AEs; 1 with unreliable medication administration from parents). The remaining 10 patients started CBD treatment less than 12 months before the chart extraction date and consequently had less than 12 months of follow-up data available. Of the 12 patients who discontinued CBD treatment because of non-efficacy, one patient was taking <10 mg/kg/day CBD, six patients were taking 10–19 mg/kg/day, and four patients were taking ≥20 mg/kg/day at withdrawal; CBD dose was not reported for one patient.

3.2. Patient demographics and baseline characteristics

Overall, 86% of patients were diagnosed with LGS and 14% of patients were diagnosed with DS (Table 1). Concomitant use of other ASMs was recorded in 77% of patients with LGS at baseline, with 21 patients having missing or invalid data; the most common medications were valproate and lamotrigine (Table 1). Concomitant use of other ASMs was recorded in 93% of patients with DS at baseline, with missing or invalid data for one patient; the most common medications were valproate and topiramate (Table 1). The mean (standard deviation; SD) time-averaged dose of CBD was 13.54 (3.89) mg/kg/day in patients with LGS and 11.56 (5.52) mg/kg/day in patients with DS.

Table 1
Demographics and baseline characteristics (full analysis set).

	LGS (n = 92)	DS (n = 15)	Total (N = 107)
Age at start of CBD without clobazam, years			
Mean (SD)	14.5 (10.3)	10.5 (4.2)	13.9 (9.7)
Median (range)	12 (2–55)	10 (5–18)	12 (2–55)
Q1, Q3	9, 16	7, 14	8, 16
Sex, n (%)			
Female	40 (44)	10 (67)	50 (47)
Male	52 (57)	5 (33)	57 (53)
Patients [n (%)]			
Reported ASMs[a]	71 (77)	14 (93)	85 (79)
Number of concomitant ASMs			
1	4 (4)	1 (7)	5 (5)
2	20 (22)	5 (33)	25 (23)
3	22 (24)	3 (20)	25 (23)
≥4	25 (27)	5 (33)	30 (28)
Most common ASMs (≥10% of patients in either group)			
Valproate	36 (39)	9 (60)	45 (42)
Lamotrigine	30 (33)	1 (7)	31 (29)
Topiramate	17 (19)	7 (47)	24 (22)
Rufinamide	15 (16)	0	15 (14)
Clonazepam	11 (12)	3 (20)	14 (13)
Zonisamide	9 (10)	3 (20)	12 (11)
Vigabatrin	11 (12)	0	11 (10)
Phenobarbital	8 (9)	2 (13)	10 (9)
Levetiracetam	5 (5)	2 (13)	7 (7)
Stiripentol	2 (2)	5 (33)	7 (7)
Mean time-averaged CBD dose (mg/kg/day)			
After 3 months	11.09 (n = 85)	10.18 (n = 15)	10.95 (n = 100)
After 6 months	13.94 (n = 85)	12.10 (n = 15)	13.66 (n = 100)
After 9 months	14.89 (n = 75)	12.16 (n = 12)	14.52 (n = 87)
After 12 months	15.19 (n = 67)	13.21 (n = 9)	14.96 (n = 76)

Percentages are calculated using the full analysis set column totals.
[a] n = 22 patients (1 DS, 21 LGS) had missing or invalid data reported for concomitant ASMs.

ASM, antiseizure medication; CBD, cannabidiol; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; Q1, first quartile; Q3, third quartile; SD, standard deviation.

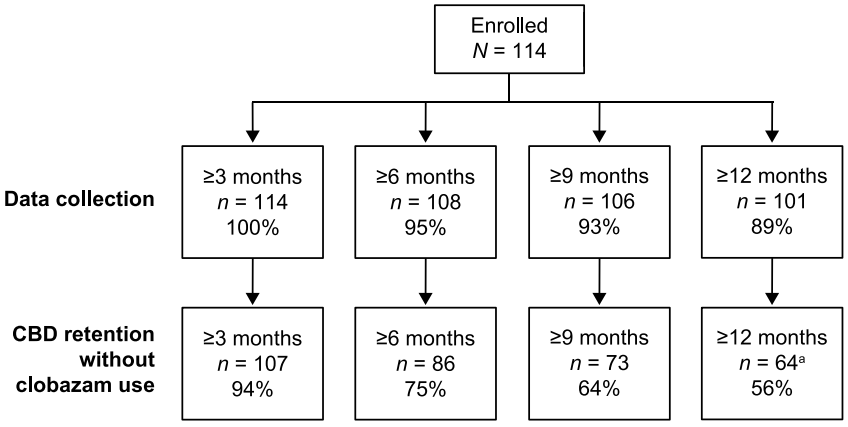


Fig. 1. Patient disposition.
Percentages are calculated from the enrolled set of patients.
[a]50 patients had <12 months of data on CBD without clobazam, including 23 who started clobazam, 16 who discontinued CBD (12 non-efficacy; 3 AEs; 1 unreliable medication administration), 10 who started CBD without clobazam <12 months before chart extraction date, and 1 with no available data.
AE, adverse event; CBD, cannabidiol.

Table 2
Median baseline seizure frequency and percentage change from baseline in drop (LGS) or convulsive (DS) seizures per 28 days (full analysis set).

		Percentage change from baseline[a] in seizure frequency per 28 days			
	Baseline	0–3 months	4–6 months	7–9 months	10–12 months
LGS: drop seizures					
n	76	69	69	58	53
Median (Q1, Q3)	33.0 (14.0, 79.7)	−6.2 (−33.3, 0.0)	−19.5 (−50.0, 0.0)	−20.9 (−50.0, 0.0)	−16.7 (−52.4, 0.0)
Range	0.0, 1260.0	−100.0, 6626.7	−100.0, 6626.7	−90.1, 6626.7	−100.0, 6626.7
DS: convulsive seizures					
n	14	14	12	9	8
Median (Q1, Q3)	7.4 (3.0, 24.0)	0.0 (−33.3, 49.8)	0.0 (−62.3, 58.9)	−16.7 (−80.3, 20.0)	0.0 (−30.2, 23.0)
Range	0.3, 112.0	−98.8, 506.1	−100.0, 203.0	−100.0, 96.5	−85.5, 58.5

[a] Among patients remaining on CBD without clobazam at each time point.
DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; Q1, first quartile; Q3, third quartile.

3.3. Effectiveness

3.3.1. Percentage change from baseline in seizure frequency

Seizure frequency data at baseline and during treatment with CBD varied considerably between patients. In patients with LGS, the median percentage change from baseline in drop seizure frequency over 0–3 and 10–12 months after starting CBD treatment without concomitant clobazam was −6.2% ($n = 69$) and −16.7% ($n = 53$) (Table 2). In patients with DS, the median percentage change from baseline in convulsive seizure frequency over 0–3 ($n = 14$) and 10–12 months ($n = 8$) after starting CBD treatment without concomitant clobazam was 0% at both time points (Table 2).

3.3.2. Achievement of ≥50% and ≥75% seizure reduction or seizure freedom

In patients with LGS remaining on CBD without concomitant clobazam at each time point, threshold achievements in drop seizure reduction at 3 months were 13/69, 19% (≥50%) and 4/69, 6% (≥75%),

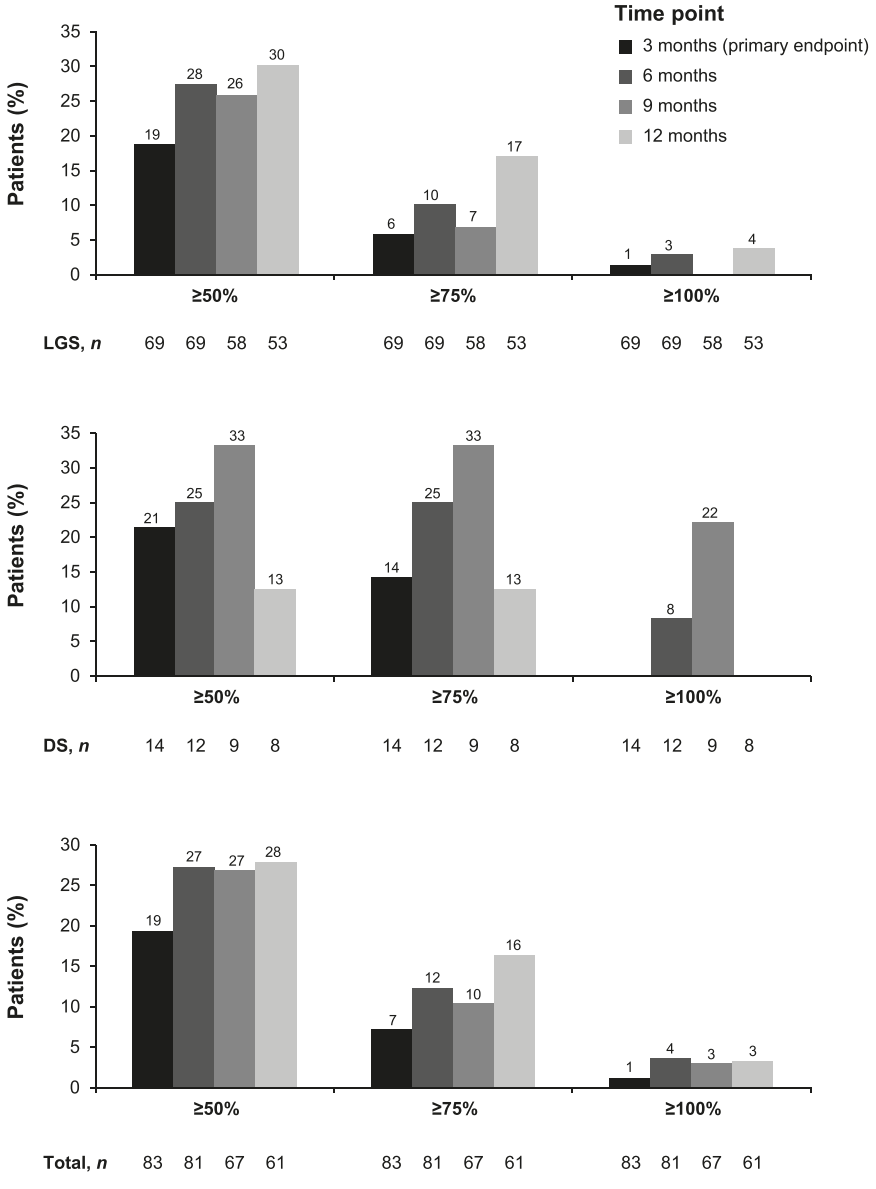
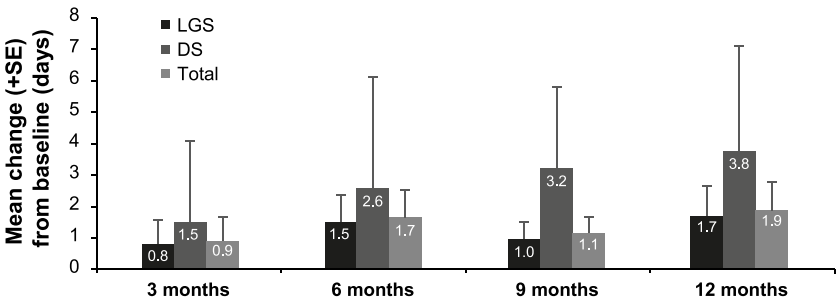


Fig. 2. Achievement of ≥50%, ≥75%, and 100% (freedom) reduction in drop (LGS) or convulsive (DS) seizures (full analysis set).
Baseline is defined as the 3-month period prior to initiation of CBD without clobazam.
Values are among the patients remaining on CBD without clobazam at each time point.
CBD, cannabidiol; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.



	3 months	6 months	9 months	12 months
LGS, *n*	58	59	49	44
DS, *n*	11	9	4	4
Total, *n*	69	68	53	48

Fig. 3. Mean (SE) change from baseline in the number of drop (LGS) or convulsive (DS) seizure-free days per 28 days (full analysis set).
Baseline is defined as the 3-month period prior to initiation of CBD without clobazam.
Values are among the patients remaining on CBD without clobazam at each time point.
CBD, cannabidiol; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; SE, standard error.

and at 12 months were 16/53, 30% (≥50%) and 9/53, 17% (≥75%) (Fig. 2). Seizure freedom in patients with LGS was reported in 1/69 (1%) patients after 3 months and 2/53 (4%) patients after 12 months of CBD treatment. In patients with DS remaining on CBD without concomitant clobazam at each time point, threshold achievements in convulsive seizure reduction at 3 months were 3/14, 21% (≥50%) and 2/14, 14% (≥75%), and at 12 months were 1/8, 13% (≥50%) and 1/8, 13% (≥75%) (Fig. 2).

3.3.3. Seizure-free days

The mean number of seizure-free days is shown in Fig. 3. The mean number of drop seizure-free days per 28 days in patients with LGS was 7.0 at baseline (n = 65). Among patients remaining on CBD without concomitant clobazam at each time point, the changes from baseline were 0.8 at 3 months (n = 58) and 1.7 at 12 months (n = 44). The mean number of convulsive seizure-free days per 28 days in patients with DS was 16.9 at baseline (n = 11). Among patients remaining on CBD without concomitant clobazam at each time point, the changes from baseline were 1.5 at 3 months (n = 11) and 3.8 at 12 months (n = 4).

3.4. Retention

Retention of CBD treatment without concomitant clobazam use in the enrolled set with available data was 107/114 (94%) at 3 months, 86/108 (80%) at 6 months, 73/106 (69%) at 9 months, and 64/101 (63%) at 12 months.

Table 3
Adverse events (full analysis set).

Patients, *n* (%)	Total (*N* = 107)
AEs	33 (31)[a]
AEs leading to permanent discontinuation	2 (2)[b]
Severe AEs	1 (1)[c]
SAEs	4 (4)[d]
AESIs[e]	10 (9)
Deaths	0

[a] 21 (20%) patients had AE(s) that were considered by the investigator to be treatment-related.
[b] 1 (1%) patient had AE(s) leading to permanent discontinuation that were considered by the investigator to be treatment-related.
[c] 1 (1%) patient had severe AE(s) that were considered by the investigator to be treatment-related.
[d] 2 (2%) patients had SAE(s) that were considered by the investigator to be treatment-related.
[e] AESIs include hepatocellular injury, somnolence, diarrhea, sedation, lethargy, pneumonia, rash, hypersensitivity reactions, suicidality, seizure worsening, aggression, euphoria, impact on cognitive development, and urinary retention.

AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event.

3.5. Safety

3.5.1. Adverse events

AEs were reported for 33 patients (31%) (Table 3). The most common AEs (≥2 patients) were somnolence (6%, n = 6), diarrhea (6%, n = 6), decreased appetite (4%, n = 4), seizure (3%, n = 3), nausea (2%, n = 2), and tooth fracture (2%, n = 2). Permanent CBD discontinuation due to an AE was observed in two patients who experienced seizure worsening.

Four patients (all with LGS) experienced SAEs. Two SAEs were considered by the investigator to be related to CBD treatment. One patient (14-year-old) experienced seizure clusters after a CBD dose increase from 14.0 to 14.6 mg/kg/day. The patient recovered following diazepam treatment; the dose of CBD was reduced to 14.0 mg/kg/day. The patient was receiving risperidone, lamotrigine, and perampanel concomitantly. Another patient (10-year-old) experienced drowsiness and hypertransaminasemia and was hospitalized with life-threatening hyperammonemia (119 μmol/L; normal range: 11–35 μmol/L) during treatment with CBD 29.4 mg/kg/day. The ammonia level returned to normal (value not available) after carglumic acid treatment, and the CBD dose was reduced to 22 mg/kg/day. The patient was receiving valproate, phenobarbital, and topiramate concomitantly. The other two SAEs were considered by the investigator to be unrelated to CBD treatment. One patient (10-year-old) tested positive for COVID-19 and the other patient (14-year-old) reported a femur fracture; the investigator suspected that this event was due to a seizure.

3.5.2. Abnormal clinical laboratory evaluations

Four patients (all with LGS) experienced at least one clinically significant laboratory abnormality during the study. One patient (35-year-old) had elevated alanine transaminase (ALT) (99 U/L; normal range: 0–55 U/L) and aspartate transaminase (AST) (65 U/L; normal range: 20–34 U/L) on Day 197. The patient was taking valproate (1500 mg/day) throughout the study period. A second patient (10-year-old) experienced elevated ALT, AST, and gamma-glutamyltransferase (GGT) levels on multiple occasions during study follow-up, including one elevated GGT level (35 U/L; normal range: 0–31) observed on Day 1; the patient was taking valproate throughout the study, with doses tapering from 800 to 500 mg/day during follow-up. Another patient (10-year-old) had abnormal AST and GGT levels at Day 137 (values not reported); no concomitant medications were reported. The fourth patient (11-year-old) had decreased potassium levels (2.9 mmol/L; normal range: 3.5–5 mmol/L) from Day 63 to Day 92; concomitant medications included rufinamide (1200 mg/day), tetrabenazine (112.5 mg/day), topiramate (150 mg/day), and vigabatrin (2000 mg/day); diazepam (3 mg/day) was added from Day 72.

4. Discussion

This retrospective chart review study was designed to evaluate the real-world independent effectiveness of CBD without concurrent clobazam by collecting data from patients with LGS or DS enrolled in an EU EAP. Patients had a mean age of 14.5 years (LGS) and 10.5 years (DS). As expected, there were more patients with LGS ($n = 92$) than with DS ($n = 15$) enrolled in the study. By sampling patients from sites in multiple countries, this study supports representation of treatment patterns across Europe and can be used to derive a general assessment of the effectiveness of CBD use without clobazam.

Our results identified that the average daily dose of CBD without clobazam was 13.5 mg/kg/day (LGS) and 11.6 mg/kg/day (DS). These doses are similar to those from the Italian EAP analyses that demonstrated the efficacy of CBD with or without clobazam in LGS and DS [25]. This analysis reported a median CBD dose of 14 mg/kg/day with no significant difference in dose between responders and non-responders [25]. However, CBD doses in our study were lower than those reported to be effective in reducing seizure frequency in analyses of US EAP data in patients with drug-resistant epilepsy [26]. This may reflect the higher maximum recommended dose of CBD in the US EAP study [26] (50 mg/kg/day vs 20 mg/kg/day in the EU EAP), which took place before a dose-defining study had been performed [27]. In our study, patients were censored from follow-up when clobazam treatment was added; therefore, no data were collected for the average dose of CBD in patients taking concomitant clobazam. However, in the US EAP, there was no significant difference in the mean CBD dose at the best point of seizure control between patients on (25.9 mg/kg/day) or off (30.1 mg/kg/day) clobazam [26].

In our study, 77% of patients with LGS were reported to be taking at least one concomitant ASM (23% had missing/invalid data) and 27% were taking four or more; the two most common ASMs were valproate and lamotrigine. Of the patients with DS, 93% were reported to be taking at least one concomitant ASM and 33% were taking four or more; the two most common ASMs were valproate and topiramate. This high number of concomitant ASMs reflects the treatment-resistant nature of the study population. Additionally, it highlights the need for individualized approaches to treatment choices and drug combinations to avoid overtreatment. It is common for a patient's quality of life to be impaired more by treatment side effects than by the seizures themselves, particularly with ASMs that have an impact on coordination, cognition, and behavior [6].

In our study, the primary endpoints were seizure data recorded over the first 3 months of treatment. After 3 months, there were small reductions in seizures for patients with LGS, but in patients with DS a notable seizure reduction was not observed after 3 months of treatment. However, seizure data were highly variable with a high proportion of missing documented data. Over the 12-month data collection period, patients with LGS had median seizure reductions of 6.2–20.9% at each time point, and 30% of patients remaining on treatment after 12 months achieved a $\geq$ 50% reduction in the number of seizures. Additionally, the change from baseline in the mean number of drop seizure-free days in patients with LGS was 1.7 days after 12 months of treatment. It should be noted that the discontinuation of CBD for non-efficacy by some patients could have caused an enrichment effect of responders over the 12-month data collection period. Therefore, it is not possible to compare the effectiveness of CBD across different time points. In contrast to patients with LGS, patients with DS had median seizure reductions of 0% at each time point, except at 7–9 months (16.7%). Nevertheless, the change from baseline in the mean number of convulsive seizure-free days in patients with DS was 3.8 days after 12 months of treatment. It is important to note that the reported seizure frequency per 28 days was widely variable at baseline (range 0–1260 in LGS and 0.3–112 in DS) and during treatment with CBD (range −100 to 6627 in LGS; −100 to 506 in DS). This has undoubtedly impacted these findings, especially given the small number of patients with DS enrolled in this study and the high proportion of missing documented data. These findings highlight the difficulties inherent in the assessment of seizure frequency owing to the inconsistent and unstandardized capture of seizure types and counts in clinical practice. Despite this, our results support subgroup analyses that demonstrated that add-on CBD was effective in reducing seizures without clobazam [22,28]. This study only includes patients taking CBD without clobazam and, therefore, no comparison with patients taking CBD with clobazam can be made. However, previous EAP studies found similar seizure reduction with CBD in patients with or without concomitant clobazam [25,26]. Additionally, we observed a potential association of CBD with an increased number of seizure-free days; a previous vignette study noted that an increase in the number of seizure-free days may improve the quality of life for both patients and caregivers [29].

Our findings revealed that a high proportion of patients with LGS or DS remained on CBD without concomitant clobazam for up to 12 months. The main reasons for CBD discontinuation within 12 months were lack of efficacy (11% enrolled set) and AEs (3% enrolled set). These findings suggest that treatment with CBD without clobazam is sustainable and tolerable. Previous analyses of EAP data indicating high retention have included patients both with and without concomitant clobazam. Among patients enrolled in the EAP in Italy, CBD retention was 68.5% in patients with at least 1 month of treatment [25]. In this cohort, CBD was discontinued in 17.2% of patients owing to lack of efficacy and 12.9% owing to AEs [25]. Another analysis of 18 adult patients with DS enrolled in the EAP in the UK found that two patients discontinued CBD before reaching 10 mg/kg/day and one patient discontinued 7 days after reaching the final dose owing to an AE. The remaining patients continued on the final dose for between 21 and 370 days [30].

In our study, CBD had an acceptable safety profile without concomitant clobazam as demonstrated in subgroup analyses of the RCTs and in an open-label study conducted in France [22,31]. The overall incidence of AEs in patients who received CBD was 31% in our study and 74–93% in the RCTs [13–16]. Although the findings from this retrospective chart review study cannot be directly compared with those from the RCTs, it should be noted that CBD was dosed according to a fixed titration and maintenance schedule in the RCTs. Notably, an open-label, multicenter study found that slower titration of CBD according to the patient's tolerance and efficacy resulted in a better tolerance while providing similar efficacy to previous trials [31]. It is also possible that AEs may be under-reported in a real-world setting. The most common AEs reported in this study were somnolence (6%), diarrhea (6%), and decreased appetite (4%), in line with those commonly observed during the phase 3 RCTs [13–16]. In a meta-analysis of data from the RCTs, some adverse events were more common in patients with concomitant clobazam, including somnolence, rash, pneumonia, and aggression [22].

In clinical trials, CBD has shown dose-related elevations of liver transaminases (ALT and/or AST) [13–16], with <1% of patients with ALT or AST levels greater than 20 times the upper normal limit [2]. Most ALT elevations occurred in patients taking concomitant valproate, but concomitant use of clobazam has also been linked with an increased incidence of transaminase elevations, although to a lesser extent than valproate [2]. In our study, at least one clinically relevant laboratory finding was reported in four patients (two taking valproate) in the LGS group and no patients in the DS group. In the RCTs, 5% of patients with LGS and 7% of patients with DS reported increased AST levels, of whom 6/11 (55%) and 13/14 (93%) were taking concomitant clobazam and 9/11 (82%) and 14/14 (100%) were taking concomitant valproate [23].

We did not investigate potential effect modification by concomitant ASMs on CBD, as this was outside the scope of this study. Concomitant use of CBD and clobazam has been shown to increase exposure of the major active metabolites of both compounds and increase the incidence of somnolence and sedation [17–19,23,32]. Also, concomitant CBD and stiripentol treatment leads to increased stiripentol exposure and a

decrease in CBD metabolites, although the clinical relevance of these changes is unknown [18,33]. Trials have reported no significant effects on the exposure of valproate or CBD following concomitant treatment [18,33].

Although steps were taken to minimize bias in patient selection and measurement, the interpretation of retrospective chart review studies is limited by the uncontrolled design, missing/incomplete data, and the variability of data collection in clinical practice [34]. Data may be incomplete for several reasons, including treatment by multidisciplinary teams or multiple sites, absence of exact information, missing reports of treatment interruptions or poor adherence, and poor capture of reasons for CBD discontinuation. Another limitation is that statistical analyses were descriptive in nature, so comparisons between treatment or patient groups were not possible. Additionally, our patient population may not represent the overall population of patients with LGS or DS since patients enrolled in the EAP were likely to have severe drug-resistant epilepsy. It should also be noted that the low number of patients with DS enrolled in this study, possibly owing to the likely concomitant treatment with clobazam [35], may impact the strength of data in this patient group. A final limitation of this study is that the use of ASMs apart from clobazam was not taken into consideration.

5. Conclusion

Despite the limitations pertaining to this real-world retrospective chart review study conducted in patients with LGS or DS in multiple clinics across multiple countries, our findings support favorable effectiveness and retention of CBD without concomitant clobazam for up to 12 months in clinical practice. This study was conducted with Epidyolex®, and results do not apply to other CBD-containing products.

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Data sharing statement

All relevant data are provided with the manuscript. Jazz Pharmaceuticals, Inc. is adhering to current US and EU requirements so will not make individual deidentified participant data available; however, the protocol and statistical analysis plan will be made available upon request to corresponding author. Jazz Pharmaceuticals, Inc. has established a process to review requests from qualified external researchers for data from Jazz-sponsored clinical trials in a responsible manner that includes protecting patient privacy, assurance of data security and integrity, and furthering scientific and medical innovation. Additional details on Jazz Pharmaceuticals, Inc. data sharing criteria and process for requesting access can be found at: https://www.jazzpharma.com/science/clinical-trial-data-sharing/

Declaration of Competing Interest

All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship or participation as a study investigator. The authors have stated the following potential conflicts of interest: RN is the Chair of the Scientific Committee of the French National Rare Diseases Database, has received consulting fees from Biocodex, UCB, Jazz Pharmaceuticals, Inc., Orion, Roche, and Takeda, and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Biocodex, UCB, Jazz Pharmaceuticals, Inc., Nutricia, and Zogenix. AA is a coordinator of the European Reference Network for Rare and Complex Epilepsies, has received consulting fees from Eisai, GW Pharmaceuticals (now part of Jazz Pharmaceuticals, Inc.), Orion Pharma, UCB, and Zogenix, payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Biocodex, Eisai, Takeda, UCB, and Zogenix, and has participated on a Data Safety Monitoring board for UCB. SA has received payment to his institution for his role as Deputy Editor for Epilepsia and has received consulting fees from GRIN Therapeutics, Jazz Pharmaceuticals, Inc., Neuraxpharm, Nutricia, Orion, Supernus, Takeda, Vitaflo, and Xenon, and received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Biocodex, BioMarin Pharmaceutical, Neuraxpharm, UCB, and Zogenix. CN and DF are full-time employees of Jazz Pharmaceuticals, Inc. who, in the course of their employment, receive stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. PP has received support for attending meetings and/or travel from Jazz Pharmaceuticals, Inc. VS has a leadership or fiduciary role at the Sociedad Española de Neuropediatria, has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Eisai, Jazz Pharmaceuticals, Inc., and UCB and support for attending meetings and/or travel from Jazz Pharmaceuticals, Inc., and has participated in Data Safety Monitoring and/or advisory board(s) for UCB. VV has received consulting fees and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Angelini Pharma, Bial, Eisai, Jazz Pharmaceuticals, Inc., Novartis, Takeda, and UCB. JHC is the Chair of the Medical Advisory Board, Dravet UK and has received consulting fees from GW Pharmaceuticals (now part of Jazz Pharmaceuticals, Inc.), Takeda, UCB, and Zogenix, and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Biocodex, UCB, and Zogenix. All other authors confirmed that they had no interests which might be perceived as posing a conflict or bias.

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