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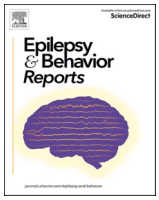

The use of cannabidiol in patients with Lennox-Gastaut syndrome and Dravet syndrome in the UK Early Access Program: A retrospective chart review study

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ABSTRACT

Purpose: To evaluate clinical outcomes from the UK Early Access Program in patients aged 2–17 years with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) treated with plant-derived highly purified cannabidiol (CBD; Epidyolex®; 100 mg/mL oral solution).

Methods: Retrospective chart review of data collected from baseline (1 month before CBD treatment initiation) until 12 months' treatment, CBD discontinuation, death, or loss to follow up.

Results: At baseline, all 26 patients enrolled (LGS, $n = 17$; DS, $n = 9$; male, 73 %; mean [range] age, 11.8 [3.0–17.0] years) experienced motor seizures; 92 % were taking ≥ 1 antiseizure medication. Median (IQR) CBD dosage at 6 months (6 M; $n = 12$) was 6.0 (2.7) mg/kg/day, and 12 months (12 M; $n = 9$) 7.3 (2.1) mg/kg/day. Median (IQR) percentage change from baseline for motor seizures was − 56.7 % (60.7) at 6 M ($n = 20$), and − 60.0 % (53.3) at 12 M ($n = 15$). Patients experiencing ≥ 50 % and ≥ 75 % reduction in motor seizures were 13/20 (65 %) and 5/20 (25 %) at 6 M, respectively, and 10/15 (67 %) and 6/15 (40 %) at 12 M, respectively. Mean (SD) motor seizure-free days/month were 1.5 (4.3) at baseline ($n = 24$, missing data $n = 2$), 2.4 (6.3) at 6 M ($n = 18$), and 2.7 (5.5) at 12 M ($n = 15$). At 12 M, CBD retention for patients with follow-up data was 14/19 (74 %), whilst 7/26 (27 %) were lost to follow up. The number of patients reporting ≥ 1 adverse event of special interest (most common: gastrointestinal) was 14/20 (70 %) and 8/15 (53 %) at 6 M and 12 M, respectively.

Conclusion: Results demonstrate a reduction in motor seizures and a safety profile consistent with previous studies.

1. Introduction

Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) are severe, lifelong epileptic encephalopathies that develop in infancy or early childhood and are often resistant to treatment [1,2]. LGS has a prevalence of ~ 1–2 % of all epilepsies and is defined by multiple drug-resistant seizures, including tonic seizures as the mandatory type, and cognitive and behavioral impairments [1,3]. Seizure onset often occurs in childhood, with a significant proportion of cases evolving from other infantile-onset epilepsy syndromes [3]. Diagnostic electroencephalogram features are diffuse slow spike-and-wave discharges (≤ 2.5 Hz) with generalized paroxysmal fast activity [1,3]. DS affects ~ 6.5/

Abbreviations: 6 M, 6 months; 12 M, 12 months; AE, adverse event; AESI, adverse event of special interest; ALT, alanine transaminase; ASM, antiseizure medication; AST, aspartate transaminase; CBD, cannabidiol; DS, Dravet syndrome; EAP, Early/Expanded Access Program; EMA, European Medicines Agency; ED, emergency department; GGT, gamma-glutamyl transferase; GOSH, Great Ormond Street Hospital; IQR, interquartile range; LFT, liver function test; LGS, Lennox-Gastaut syndrome; RCT, randomized controlled trial; SCH, Sheffield Children's Hospital; SD, standard deviation; VNS, vagus nerve stimulation.

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100,000 live births and is characterized by prolonged febrile and afebrile, focal clonic, or generalized clonic seizures that are often triggered by fever or illness in the first year of life [2,4]. Developmental regression and cognitive and behavioral impairments manifest from the second year of life of patients with DS [2], and over 80 % of cases are associated with pathogenic variants in the sodium channel gene *SCN1A*, which correspond to 0.17 % of all epilepsies [4–6].

Although the seizures associated with these syndromes are typically refractory to treatment [7–10], there are various therapeutic options available, including pharmacological and non-pharmacological treatments. These include antiseizure medications (ASMs), ketogenic diet therapy, vagus nerve stimulation (VNS), and, in suitable candidates, epilepsy surgery [7–10]. In addition to drug resistance, challenges to the treatment of LGS and DS include the high likelihood of polypharmacy and the requirement to balance the beneficial effects of ASMs with their tolerability and adverse events (AEs) [7,8,10]. Therefore, currently available treatments are unlikely to lead to sustained seizure remission in most patients, and the overall aim is to optimize seizure control and improve the learning, behavior, and overall quality of life of patients [7,10].

In four randomized controlled trials (RCTs), highly purified cannabidiol (CBD; Epidiolex® in the USA and Epidyolex® in the UK, EU, and Australia) demonstrated efficacy in the reduction of drop (LGS) and convulsive (DS) seizure frequency with an acceptable safety profile in patients with LGS or DS, alongside concomitant ASMs [11–14]. Subsequently, the European Medicines Agency (EMA) approved CBD in the UK and EU in September 2019 for the treatment of seizures associated with LGS or DS, in conjunction with clobazam, in patients ≥ 2 years of age; it is additionally approved in the UK and EU for patients ≥ 2 years of age with tuberous sclerosis complex [15,16].

Prior to regulatory approval, some patients with LGS and DS were offered early access to CBD through an Early/Expanded Access Program (EAP). The EAP was available in various countries, including some European countries and the USA. In the UK, the EAP was launched in November 2018 and was most likely to have been utilized by clinicians for treatment-refractory patients with an urgent need for alternative treatment. Patients were selected for CBD treatment according to locally defined criteria with no requirement for patients to be taking concomitant clobazam, which is now specified in the EMA label [15].

This study was a retrospective chart review of children and adolescents with LGS or DS who received CBD at two UK sites as part of the EAP. The primary objectives were to describe the treatment patterns and clinical outcomes of patients with LGS and DS enrolled in the UK EAP. These data provide a unique UK perspective to support previous publications of CBD EAPs from Europe and the USA in either treatment-resistant epilepsies, or in LGS and DS.

2. Methods

2.1. Patients

This retrospective chart review study included patients aged 2–17 years with a confirmed diagnosis of LGS or DS. Patients were required to have received CBD treatment as part of the UK EAP at either Great Ormond Street Hospital (GOSH) for Children NHS Foundation Trust or Sheffield Children's Hospital (SCH) NHS Foundation Trust. Initiation of CBD treatment in the UK EAP ran from November 1, 2018, to October 31, 2019, at GOSH and from June 1, 2019, to January 31, 2020, at SCH. All eligible patients enrolled in the EAP at each center were included in the study.

Owing to limited availability for enrollment in the EAP, patients were considered for inclusion on a case-by-case basis by the local pediatric epilepsy and neurology teams based on the appropriateness of CBD treatment and clinical urgency. At GOSH, patients were considered if they had failed at least two ASMs at adequate dosage, were not candidates for epilepsy surgery, VNS, or ketogenic diet, and had a significant seizure burden. A significant seizure burden was defined as ≥ 4 seizures per week with motor manifestations such as tonic, tonic-clonic, and atonic and that required inpatient treatment, less frequent seizures with severe compromising manifestations associated with high risk for morbidity/mortality, ≥ 1 episode of seizure escalation over a 3–6-month period requiring hospital attendance and/or admission, or frequent requirement for emergency seizure medication. At SCH, patients with confirmed LGS or DS were eligible if they had seizures refractory to at least three ASMs with motor seizures on > 3 days per week. Patients with prior epilepsy surgery, VNS, or ketogenic diet treatments were also eligible.

Patients selected for the UK EAP were prescribed plant-derived highly purified CBD medicine (Epidyolex® 100 mg/mL oral solution) and were treated following the standard clinical practice for patients with LGS or DS in each study center. All directions for medication usage and patient monitoring were solely at the discretion of the patient's treating physician. The typical starting dosage of CBD in the EAP at the study centers was 2 mg/kg/day, which was increased by 2 mg/kg/day per week. A target maintenance dosage of 10 mg/kg/day was reached after 5 weeks and could be increased until seizures were reduced. This EAP was conducted with Epidyolex®, and results do not apply to other CBD-containing products.

2.2. Ethics approval

The study was conducted following the principles of Good Pharmacoepidemiology Practice. Ethical and regulatory approval for the conduct of this study was obtained from the South Central – Berkshire Research Ethics Committee on 03/12/2021 [reference no. 21/SC/0414] and the Health Research Authority on 17/12/2021. The collection of data and the secondary use of data were completed in accordance with local and national applicable laws and regulations governing the processing of data. While a signed informed consent form was required for patients to participate in the UK EAP, no additional consent was sought for the retrospective analysis of the deidentified patient data, and an informed consent form waiver was completed per local regulations.

2.3. Data collection

The medical records of all eligible patients included in the UK EAP were reviewed in depth, and deidentified data were entered into a bespoke study electronic case report form by research staff at each center. Training sessions were provided at each center to ensure consistency in data extraction. Chart data were collected retrospectively from baseline until the end of a 12-month treatment period, or less if patients were lost to follow up or discontinued CBD, or in the event of death. The end of the study observation period was January 31, 2021, to allow for at least 12 months of follow up for each patient. The index date was defined as the start date of CBD treatment, and the baseline period was defined as the 1-month period preceding the index date. The type and frequency of seizures were described within the 1-month baseline period and over 3-month intervals during treatment with CBD.

Primary endpoints were time to discontinuation of CBD and seizure data collected over 3-month intervals, including percentage change from baseline in seizure frequency, proportion of patients with ≥ 50 %, ≥ 75 %, and 100 % reduction from baseline in seizure frequency, and number of seizure-free days per month. Seizure data were preferentially collected from patient seizure diaries or were otherwise obtained from patient notes recorded from patients or carers during follow-up visits. Motor seizures were classified as tonic, clonic, tonic-clonic, or atonic seizures. Non-motor and difficult-to-quantify (described in the case report form as difficult to quantify) seizures included atypical absence, focal with non-motor manifestations, absence, myoclonic seizures, or spasms.

Secondary endpoints included CBD dosage changes, percentage of patients still taking CBD at 3, 6, 9, and 12 months, rescue medication

use, concomitant ASMs, recorded hospitalizations (≥ 1 overnight stay) or emergency department (ED) visits due to epilepsy, and incidence of adverse events of special interest (AESI). Only AESIs were collected in this study; categories were informed by the EMA Epidyolex® summary of product characteristics [15] and included gastrointestinal (diarrhea, constipation, vomiting), general (fatigue, pyrexia, rash, hypersensitivity reactions, suicidality, aggression, euphoria), infections (pneumonia, nasopharyngitis), metabolism (decreased appetite, weight gain), nervous system (somnolence, status epilepticus, impact on cognitive development), liver injury or abnormal results on liver function tests (LFTs; alanine transaminase [ALT], aspartate transaminase [AST], gamma-glutamyl transferase [GGT]), and urinary retention. At GOSH, liver function testing was required 2 weeks after each dosage adjustment and every 3 months thereafter or on the occurrence of a clinical event. At SCH, liver function testing was performed during fortnightly blood monitoring.

2.4. Statistical analysis

All statistical analyses were descriptive in nature using SAS® version 9.4. Data for patients with LGS or DS were combined into an overall population owing to the small sample size. Patient numbers refer to those with available data at each timepoint. Unavailable data at each timepoint may be a result of missing data, no clinic visit at that timepoint, or the patient being lost to follow up.

3. Results

3.1. Patient disposition

Overall, 26 patients were enrolled in the study and all contributed chart data at index. The number of patients with available data at each timepoint was 24/26 (92 %) at 3 months, 20/26 (77 %) at 6 months, 19/26 (73 %) at 9 months, and 15/26 (58 %) at 12 months (Fig. 1). Over the 12-month period, seven patients were lost to follow up, and five patients discontinued CBD (Fig. 1). The mean (standard deviation) follow-up duration from the index date was 10.6 (3.2) months.

3.2. Baseline characteristics

Of the 17 patients with LGS, seven were at GOSH, and ten were at SCH. Of nine patients with DS, seven were at GOSH, and two were at SCH. All patients with DS had seizure onset before the age of 1 year, while patients with LGS had a wider age range of seizure onset (Table 1). All patients had experienced motor seizures, and most patients had a high seizure burden and/or cognitive impairment and/or were taking at least one ASM (Table 1). The most common ASMs reported at baseline (n = 26) were rufinamide (53 %), clobazam (41 %), and valproate (35 %) in patients with LGS, and clobazam (78 %), stiripentol (56 %), and valproate (44 %) in patients with DS (Table S1). Furthermore, 38 % of patients at baseline required ≥ 1 rescue medication: 15 % weekly buccal midazolam and 19 % monthly buccal midazolam. One patient was also recorded, per protocol, as requiring daily clobazam as a rescue medication according to the treating physician (Table 1).

3.3. CBD dosage

Of patients with recorded weight, the median (range) CBD dosage at 3 (n = 14), 6 (n = 12), 9 (n = 8), and 12 months (n = 9) was 6.1 (0.5–10.0), 6.0 (0.5–11.5), 8.7 (3.3–10.3), and 7.3 (1.0–11.5) mg/kg/day, respectively. Weight data were missing for 10/24, 8/20, 11/19, and 6/15 patients at 3, 6, 9, and 12 months, respectively, so the CBD dosage by weight could not be calculated for these patients.

3.4. Time to CBD discontinuation and CBD retention rate

Five patients discontinued CBD over the 12-month period. The first patient discontinued between baseline and the 3-month follow-up visit because the patient refused to take the medication. Between 6 and 9 months of CBD treatment, three patients discontinued CBD owing to lack

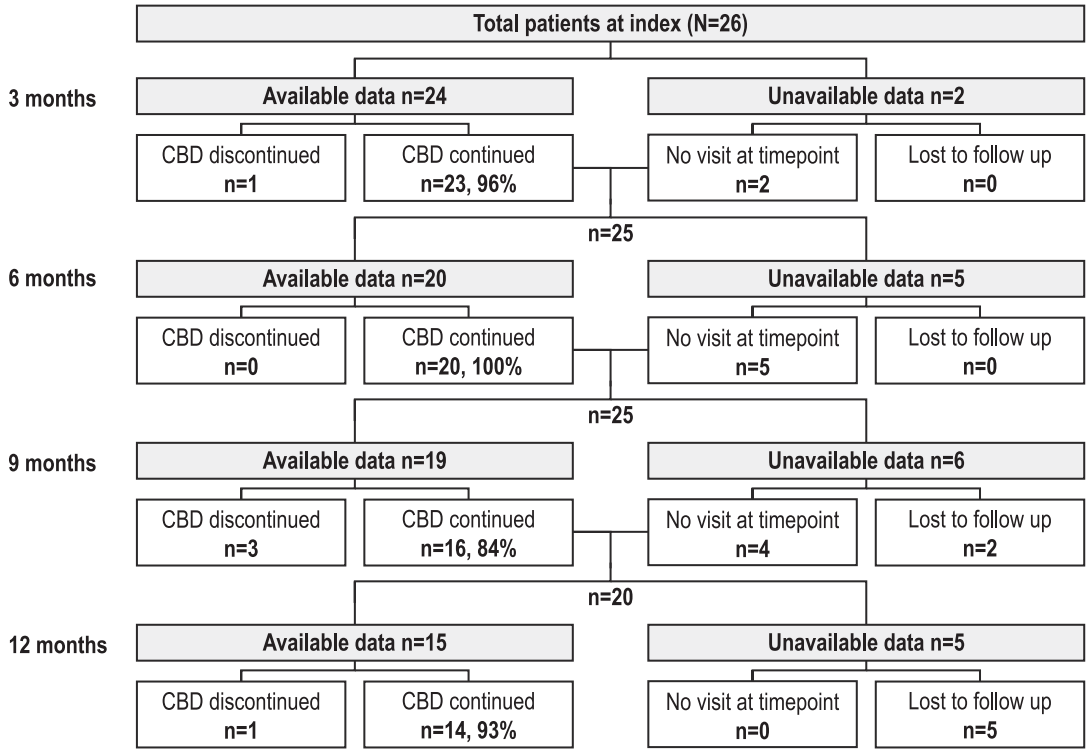

Fig. 1. Patient disposition.
The percentage of patients who continued CBD was calculated using the available data for each timepoint as the denominator. CBD, cannabidiol.

Table 1
Patient demographic and baseline clinical characteristics.

	LGS ($n = 17$)	DS ($n = 9$)
Age at first seizure (years), mean (range)	2.8 (0.1–10.0)	0.4 (0.1–0.9)
Age at diagnosis of LGS or DS (years), mean (range)	5.8 (0.3–12.0)	3.4 (0.1–11.0)
Age at CBD initiation (index) (years), mean (range)	13.0 (10.0–17.0)	9.4 (3.0–16.0)
At least one ASM, *n* (%)	16 (94)	8 (89)
Clobazam	7 (41)	7 (78)
	All patients ($N = 26$)	
Male, *n* (%)	19 (73)	
Seizure types, *n* (%)		
Motor seizures	26 (100)	
Non-motor and difficult-to-quantify seizures	20 (77)	
Seizure frequency per week, median (range)		
Motor seizures	70.0 (3.0–350.0)	
Non-motor and difficult-to-quantify seizures	35.0 (0–350.0)	
Cognitive function impairment, *n* (%)	25 (96)	
Need for ≥ 1 rescue medication in the month prior to index, *n* (%)	10 (38)	
Weekly buccal midazolam	4 (15)	
Monthly buccal midazolam	5 (19)	
Daily clobazam[a]	1 (4)	
Interventions in the month prior to index, *n* (%)		
Ketogenic diet	3 (12)	
VNS	7 (27)	
Surgery	0	
Hospitalization due to epilepsy in the month prior to index, *n* (%)	3 (12)	
ED visit due to epilepsy in the month prior to index, *n* (%)	2 (8)	

[a]Recorded, per protocol, as a rescue medication according to the treating physician.
ASM, antiseizure medication; CBD, cannabidiol; DS, Dravet syndrome; ED, emergency department; LGS, Lennox-Gastaut syndrome; VNS, vagus nerve stimulation.

of effectiveness. The final patient discontinued CBD between 9 and 12 months and cited lack of effectiveness. Kaplan-Meier analysis of patients with follow-up data calculated the probability of patients remaining on CBD treatment over 12 months as 0.737 (Fig. S1). After 12 months, the number of patients with available CBD retention data was 19/26 (73 %). Of these patients, the retention rate was 74 % (14/19).

3.5. Change in seizure frequency and responder rate

The number of patients with seizure data derived from a seizure diary was 11/26 (42 %), 10/24 (42 %), 6/20 (30 %), 8/19 (42 %), and 6/15 (40 %) at baseline, 3, 6, 9, and 12 months, respectively. All remaining seizure data were collected using subjective recall from patients or carers at follow-up visits.

Over 12 months, there was an observed reduction in the number of both motor and non-motor and difficult-to-quantify seizures per month, and over half of patients achieved ≥ 50 % reduction in seizure frequency per month after 12 months of CBD treatment (Fig. 2).

3.6. Seizure-free days

The mean number of seizure-free days is shown in Fig. 3. Over 12 months, the mean number of motor and non-motor and difficult-to-quantify seizure-free days was higher than baseline at each timepoint. Data were missing for two patients at baseline, three patients at 3 months, two patients at 6 months, and two patients at 9 months.

3.7. Rescue medication use

Rescue buccal midazolam was required by 13–31 % of patients with LGS and 43–67 % of patients with DS at all timepoints (Table 2). Monthly rescue rectal diazepam was required by one patient with LGS at 6 months and one patient with LGS at 9 months.

3.8. Concomitant ASM use

The number of patients taking clobazam was 14/26 (54 %), 7/24 (29 %), 8/20 (40 %), 11/19 (58 %), and 9/15 (60 %) at baseline, 3, 6, 9, and 12 months, respectively, with some patients initiating or discontinuing clobazam during the study. The number of patients taking valproate, stiripentol, and rufinamide at baseline was 10/26 (38 %), 6/26 (23 %), and 9/26 (35 %), respectively. After 12 months of CBD treatment, these ASMs were used by 2/15 (13 %), 2/15 (13 %), and 4/15 (27 %) patients, respectively.

3.9. Hospitalizations and ED visits

The number of patients with recorded hospitalizations (≥ 1 overnight stay) due to epilepsy was 4/24 (17 %), 3/20 (15 %), 2/19 (11 %), and 3/15 (20 %) at 3, 6, 9, and 12 months, respectively. The number of patients with reported ED visits due to epilepsy was 3/24 (13 %), 0, 2/19 (11 %), and 0/15 (0 %) at 3, 6, 9, and 12 months, respectively.

3.10. Adverse events of special interest

AESIs were reported in over 50 % of patients at each timepoint (Table 3). The most common AESIs reported were gastrointestinal (diarrhea, constipation, vomiting), general (fatigue, pyrexia, rash, hypersensitivity reactions, suicidality, aggression, euphoria), and liver injury / abnormal LFTs (ALT, AST, or GGT). No AESIs resulted in CBD discontinuation.

4. Discussion

This study provides further useful information on treatment patterns and outcomes of patients with LGS and DS treated with CBD within the UK EAP. Previous evaluations of EAPs have been published from Italy, Spain, and the USA in pediatric and adult patients with various treatment-resistant epilepsies [17–20], and from France, Germany, Italy, Spain, the UK, and the USA in patients with LGS or DS taking CBD with or without concomitant clobazam [21–23]. The novel findings of this study, based on data from the perspective of two UK centers, align with previous publications from Europe and the USA, further supporting the effectiveness of CBD in reducing motor seizures and maintaining a consistent safety profile in patients with LGS and DS, with and without clobazam use [21–23].

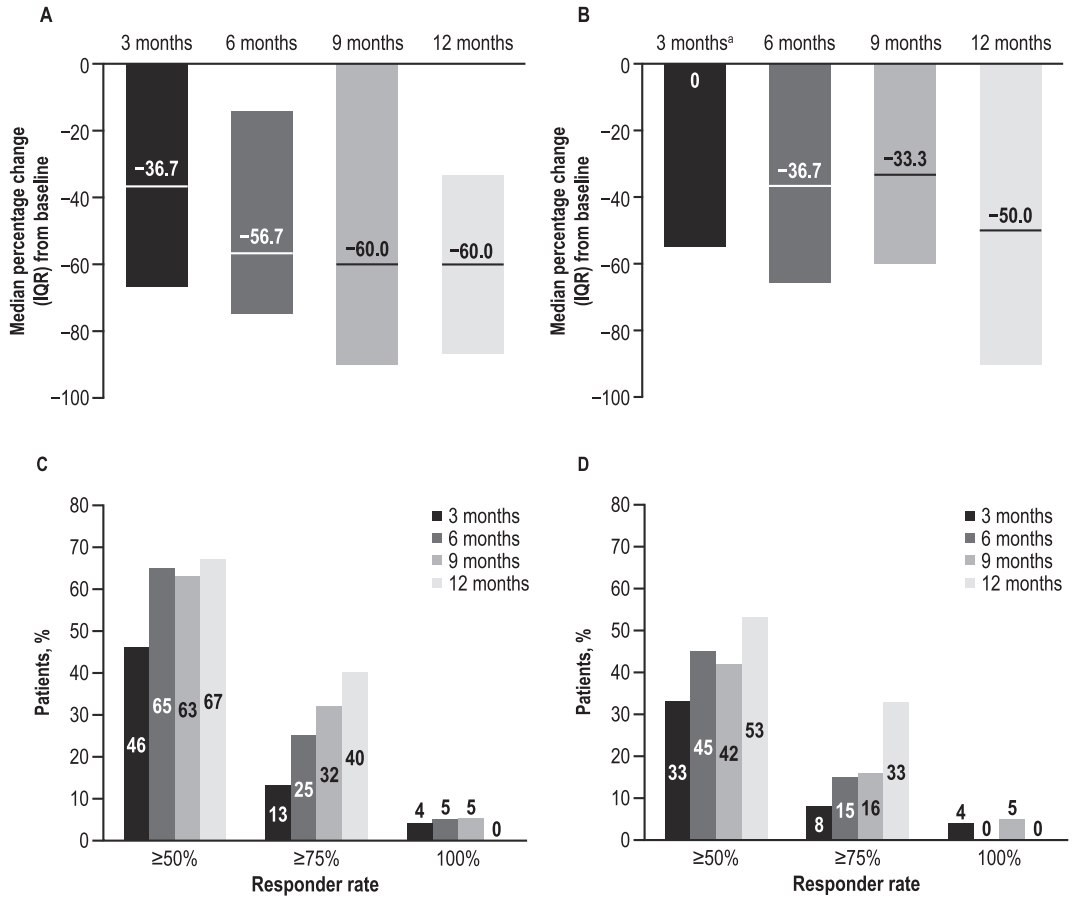

Fig. 2. Median percentage change from baseline (IQR) in motor **(A)** and non-motor and difficult-to-quantify **(B)** seizure frequency per month. ≥ 50 %, ≥ 75 %, and 100 % responder rates for motor **(C)** and non-motor and difficult-to-quantify **(D)** seizures. [a]The median percentage change from baseline in non-motor and difficult-to-quantify seizure frequency per month at 3 months was zero.
In A and B, the upper and lower bounds of the box represent quartile 1 and quartile 3, and the central line represents the median. IQR, interquartile range.

Patients with LGS and DS selected for the UK EAP presented at the more severe end of the clinical spectrum, with a high seizure burden refractory to previous treatments. At baseline, all patients experienced motor seizures, most had cognitive function impairment, the majority were taking ≥ 1 ASM, and 38 % required ≥ 1 rescue medication. Concomitant clobazam use was recorded for 41 % of patients with LGS and 78 % of patients with DS. This patient cohort was, therefore, similar to other EAP cohorts enrolling patients with refractory epileptic seizures, such as LGS and DS, where many patients were taking ≥ 3 ASMs [17,20–23].

The median CBD dosages reported in this study (6–9 mg/kg/day) were lower than the recommended dosage of 10–20 mg/kg/day [15,16], which may be owing to physician conservatism when using CBD before regulatory approval. However, these data are limited by missing weight information in many patients, possibly owing to the restriction of face-to-face visits during the coronavirus pandemic, and as such, should be interpreted with caution. It is also worth considering that, given that this study was conducted before EMA approval, the CBD titration schedule at both UK EAP centers was slower than the current EMA label, which recommends a starting dosage of 5 mg/kg/day increased by 5 mg/kg/day per week based on individual clinical response and tolerability [15]. Previous studies of EAPs have reported higher average CBD dosages of 10–25 mg/kg/day [17–20].

Baseline seizure frequency was high and variable, with a median (range) of 70 (3–350) motor seizures per week and 35 (0–350) non-motor and difficult-to-quantify seizures per week. It is important to note that the non-motor and difficult-to-quantify seizure data are less reliable than motor seizure data, given the difficulty in accurate counts and possible variance between caregiver reporting during clinic visits. After 12 months of CBD treatment, the median percentage change from baseline in motor seizure frequency was − 60 %, and in non-motor and difficult-to-quantify seizure frequency was − 50 %. This aligns with other EAP analyses, although these studies report a median total seizure frequency reduction of 46–66 % [18,20]. In our study, over half of patients achieved ≥ 50 % reduction in motor seizures per month after 12 months of CBD treatment. Previous uncontrolled studies of EAPs have similar findings, reporting that 49 % of patients achieved a ≥ 50 % reduction in total seizure frequency per month after 52–144 weeks of CBD treatment [17,19]. However, direct comparison with previous studies is limited because of differences in seizure outcome measures and the use of alternative seizure type categories such as convulsive and total seizures [17,20], drop (LGS) or convulsive (DS) seizures [22,23], or total seizures [21].

In this study, patients/caregivers indicated at baseline that they rarely experienced days without any seizures. There was an indication of a modest increase in the number of seizure-free days with CBD treatment at each follow-up visit, although these findings are limited by missing data and the difficulty to reliably observe or record non-motor and difficult-to-quantify seizures. However, another recent EAP study of patients taking CBD without concomitant clobazam also reported an increase from baseline in the number of seizure-free days of 1.9 days per 28 days at 12 months [22]. It is important to note that a reduction in seizure-free days was found to be a clinically meaningful outcome measure in a post-hoc analysis of the CBD RCTs [24]. Overall, these findings provide further support for the effectiveness of CBD treatment in patients with LGS and DS.

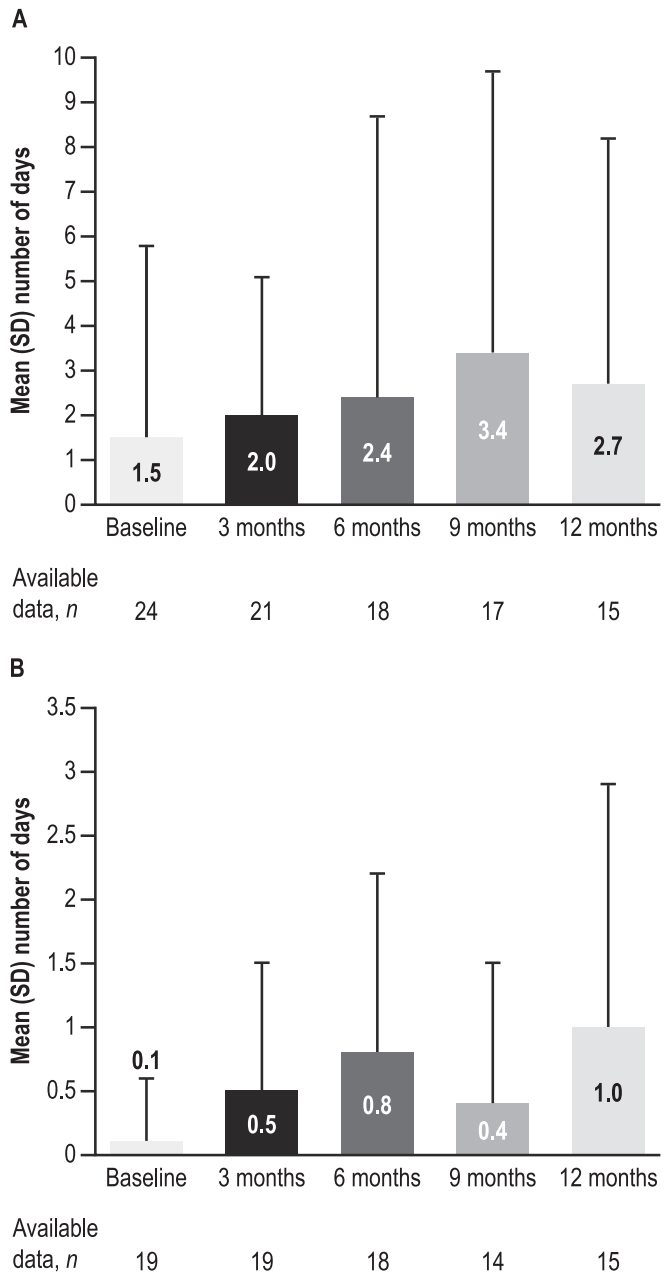

Fig. 3. Number of days per month free of motor and non-motor and difficult-to-quantify seizures. SD, standard deviation.

Of the patients with available data at 12 months (19/26, 73 %), 74 % remained on CBD treatment. In our study, 5/19 (26 %) patients with available data discontinued CBD within 12 months owing to lack of effectiveness ($n = 4$) and refusal to take the medication ($n = 1$). Other studies of EAPs have reported CBD discontinuation rates of 7–13 % owing to AEs [17–20], and one study reported discontinuation of 26 % owing to both AEs and lack of efficacy [18]. Despite the number of patients lost to follow up (7/26 [27 %]) limiting the comparability with published studies, our observations in children and adolescents with highly refractory LGS and DS indicate a similar retention to that observed in a broader population of children and adults with treatment-resistant epilepsy [17,18].

Over the 12-month period, the overall use of concomitant ASMs, including valproate, stiripentol, and rufinamide, reduced over time. The number of patients taking clobazam appeared to remain consistent, although some patients initiated or discontinued clobazam during the study. These findings are consistent with an EAP study that demonstrated concomitant ASM use remained stable or decreased over 4 years with CBD treatment in most patients with treatment-resistant epilepsies [20]. Moreover, in our study, the use of rescue medication remained relatively stable throughout. It was observed that rescue medication use was much higher in the DS group than in the LGS group. These findings may reflect the higher risk of prolonged seizures and, therefore, the larger requirement for rescue medication in patients with DS than in those with LGS [2,10].

The number of hospitalizations and ED visits remained relatively stable throughout this study, although data may be incomplete, and visits may not have been documented for all patients. A previous study of an EAP in Spain reported a trend toward reduced healthcare resource utilization after treatment with CBD based on the number of ED visits [18]. Conversely, a non-EAP retrospective chart review study found no difference in seizure-related ED visits or hospital admissions in patients with treatment-resistant epilepsy treated with CBD [25]. However, subgroup analysis of patients with a history of hospitalization prior to CBD treatment found a significant reduction in the number of hospital admissions after CBD initiation [25]. These variable findings suggest that analyses of hospitalization / ED visits from EAP data should be interpreted with caution.

Table 2
Rescue buccal midazolam use.

Patients with LGS					
	Baseline $n = 17$	3 months $n = 16$	6 months $n = 13$	9 months $n = 12$	12 months $n = 11$
Use of buccal midazolam, *n* (%)	3 (18)	2 (13)	4 (31)	3 (25)	2 (18)
Frequency, *n* (%)					
Daily	0	0	0	0	0
Weekly	1 (33)	0	0	0	0
Monthly	2 (67)	2 (100)	4 (100)	3 (100)	2 (100)
Patients with DS					
	Baseline $n = 9$	3 months $n = 8$	6 months $n = 7$	9 months $n = 7$	12 months $n = 4$
Use of buccal midazolam, *n* (%)	6 (67)	5 (63)	4 (57)	3 (43)	2 (50)
Frequency, *n* (%)					
Daily	0	0	0	0	0
Weekly	3 (50)	1 (20)	2 (50)	3 (100)	0 (0)
Monthly	3 (50)	4 (80)	2 (50)	0	2 (100)

DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

Table 3
Adverse events of special interest.

Patients, *n* (%)	3 months $n = 24$	6 months $n = 20$	9 months $n = 19$	12 months $n = 15$
At least one AESI	14 (58)	14 (70)	11 (58)	8 (53)
Gastrointestinal[a]	9 (38)	10 (50)	6 (32)	2 (13)
General[b]	6 (25)	4 (20)	6 (32)	5 (33)
Liver injury or abnormal LFT[c,d]	4 (17)	6 (30)	2 (11)	0
Metabolism[e]	1 (4)	4 (20)	2 (11)	3 (20)
Nervous system[f]	1 (4)	3 (15)	2 (11)	2 (13)
Infections[g]	0	1 (5)	1 (5)	0
Urinary retention	0	0	0	1 (7)

[a]Diarrhea, constipation, vomiting. [b]Fatigue, pyrexia, rash, hypersensitivity reactions, suicidality, aggression, euphoria. [c]Liver enzyme elevations and liver injury were captured as a single term, and we did not capture whether any cases met Hy's law, indicating severe liver injury [26]. [d]ALT, AST, or GGT outside the upper limit of normal. [e]Decreased appetite, weight gain. [f]Somnolence, status epilepticus, impact on cognitive development. [g]Pneumonia, nasopharyngitis.
AESI, adverse event of special interest; ALT, alanine transferase; AST, aspartate transferase; GGT, gamma-glutamyl transferase; LFT, liver function test.

The collection of AEs in this study focused on those of particular medical concern identified in the EMA Epidyolex® summary of product characteristics [15]. Overall, the incidence of AESIs was consistent over 12 months; patients with at least one AESI ranged from 53 % to 70 % at each timepoint, and no AESIs resulted in CBD discontinuation. Previous studies of EAPs have reported a similar incidence of all AEs, with 52–88 % of patients reporting an AE [17–20]. Alternatively, in the RCTs, AE incidence was higher than in this study and varied from 63 % to 93 % in patients treated with 10–20 mg/kg/day CBD and 69 % to 90 % in patients treated with placebo [11–14]. However, AEs tend to be reported more frequently in clinical trials than in clinical practice, and this study only reported AESIs. In this study, AESIs affecting the gastrointestinal system, general AESIs (fatigue, pyrexia, rash, hypersensitivity reactions, suicidality, aggression, euphoria), and abnormal LFTs were among the most commonly reported, which is in line with those observed in the RCTs [11–14]. Since AESI data were collected in grouped categories in this study, the frequencies of individual AESIs are not available. Liver enzyme elevations and liver injury were captured as a single term, and we did not capture whether any cases met Hy's law, indicating severe liver injury [26]. It is important to highlight that the frequency of gastrointestinal and liver enzyme AESIs was higher at 3–6 months than at 9–12 months, supporting previous claims that these AESIs may occur more frequently at the start of CBD treatment and resolve within 14 weeks [27–29].

There are several limitations to this chart review study. Firstly, the uncontrolled and retrospective nature of this observational study lends itself to a lack of a comparator, missing/incomplete data, and variability in data collection [30]. Secondly, the limited availability to prescribe CBD as part of the UK EAP biased patient selection toward those with highly refractory disease, so the response and tolerability of CBD in this population may not be representative of all patients with LGS and DS. Another key limitation of this study is that analyses were descriptive in nature, and because of the small sample size, data for patients with LGS and DS were analyzed as a combined group, which does not allow for individual analysis of each syndrome. The number of patients lost to follow up ($n = 7$) may have also impacted the data because the CBD retention rate calculation did not include these patients. Seizure frequency data may be subject to bias since most data were collected by subjective recall from patients or carers at follow-up visits rather than a formal seizure diary. Other factors that may have impacted seizure data were the large range of baseline seizure frequency and missing data on the number of seizure-free days; this reflects the difficulty in retrospectively collecting seizure data. AE reporting focused only on AESIs, which were grouped into categories; therefore, all potential AEs may not have been captured, and the incidence of important individual AEs, such as status epilepticus or suicidality, is not available. Lastly, the small number of patients enrolled in the UK EAP is a key limitation of the study; a larger cohort study is required to confirm the findings.

5. Conclusion

In this retrospective chart review study of a small cohort of patients treated with CBD, the results demonstrate a reduction in motor seizures and a safety profile consistent with that seen in other EAPs and RCTs.

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CRediT authorship contribution statement

Christin Eltze: Writing – review & editing, Methodology, Investigation, Conceptualization. **Shaikha Alshehhi:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Aisha Al Ghfeli:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Kishan Vyas:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Seeta Saravanai-Prabu:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Gaelle Gusto:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Artak Khachatryan:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Marta Martinez:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Archana Desurkar:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CE, AAG, SA, and AD have no potential conflicts of interest to disclose. KV and SS-P are employees of Jazz Pharmaceuticals UK Ltd and may hold stock and/or stock options in Jazz Pharmaceuticals plc. GG, AK, and MM are employees of Certara, which has received consulting fees from Jazz Pharmaceuticals, Inc.

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Author contributions

All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship.

Ethical statement

The study was conducted following the principles of Good Pharmacoepidemiology Practice. Ethical and regulatory approval for the conduct of this study was obtained from the South Central – Berkshire Research Ethics Committee on 03/12/2021 [reference no. 21/SC/0414] and the Health Research Authority on 17/12/2021. The collection of data and the secondary use of data were completed in accordance with local and national applicable laws and regulations governing the processing of data. While a signed informed consent form was required for patients to participate in the UK EAP, no additional consent was sought for the retrospective analysis of the deidentified patient data, and an informed consent form waiver was completed per local regulations.

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 the corresponding author. Jazz Pharmaceuticals, Inc. has established a process to review requests from qualified external researchers for data from Jazz-sponsored studies 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 the process for requesting access can be found at: https://www.jazzpharma.com/science/clinical-trial-data-sharing/.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2024.100731.

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