

## Research Paper

# Real-world effectiveness and tolerability of highly purified cannabidiol in patients with monogenic developmental and epileptic encephalopathies with highly active epilepsy

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## 1. Introduction

Developmental and epileptic encephalopathies (DEEs) represent a group of disorders characterized by developmental slowing or regression together with seizures, that are often drug-resistant.<sup>1</sup>

The cumulative incidence of DEEs has been recently estimated at approximately 169 per 100,000 children, with infantile epileptic spasms syndrome, epilepsy with myoclonic-astonic seizures, Lennox-Gastaut syndrome (LGS), and Dravet syndrome (DS) among the most common syndromes.<sup>2</sup> Given the substantial burden of disability associated with these syndromes, efforts by the scientific community and pharmaceutical companies in recent years have focused on developing new anti-seizure medications (ASMs) for these patients.

With this objective, the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) recently approved highly purified cannabidiol (CBD) for DS, LGS, and tuberous sclerosis complex (TSC)-related epilepsy. Following the randomized controlled trials that led to CBD approval,<sup>3–5</sup> numerous real-world studies have increasingly suggested effectiveness in other DEEs, particularly those of genetic origin.<sup>6–8</sup> However, most data combine patients with a wide range of seizure frequencies, and it is unclear whether individuals with very high seizure burden benefit to a similar extent as those with less active epilepsy.

In patients with DEEs, seizures are typically pleomorphic and occur at high frequency, with many individuals continuing to experience daily seizures even in the long term.<sup>9</sup> Persistent frequent seizures remain a major challenge in the management of DEEs and, depending on the developmental stage and underlying aetiology, can be associated with disruption of developmental trajectories, stagnation or loss of previously acquired skills. These effects extend to caregivers, contributing to substantial psychological distress.<sup>10,11</sup> High seizure burden further contributes to morbidity and mortality, including a heightened risk of sudden unexpected death in epilepsy (SUDEP).<sup>12,13</sup> Previous studies have identified a threshold of  $\geq 20$  seizures per month as a marker of poorer prognosis and less favorable treatment outcome.<sup>14,15</sup>

These considerations underscore the need for therapies that can substantially reduce seizure burden in this population, particularly in patients with highly active epilepsy.

With this background, we investigated the effectiveness and tolerability of highly purified CBD in a cohort of monogenic DEEs, focusing on patients with highly active epilepsy.

## 2. Methods

## Study design

In this retrospective, multicentre observational study, we identified patients with DEEs who had been prescribed highly purified CBD between May 2019 and March 2024 at 27 international specialized epilepsy centres for adults or children. Part of this cohort has been included in a previous real-world study of CBD in monogenic epilepsies.<sup>7</sup>

The study was approved by the regional ethical committee (Approval No. 7671, 0534/2024), and informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and following the STROBE guidelines for observational

studies.

Inclusion criteria were: 1) a diagnosis of a DEE attributable to a monogenic aetiology, confirmed by the presence of a pathogenic or likely pathogenic variant classified according to American College of Medical Genetics and Genomics (ACMG) criteria<sup>16</sup>; 2) treatment with  $> 99\%$  highly purified CBD (Epidiolex – Jazz Pharmaceuticals, UK- for patients treated in European countries, Convupidiol – Alef Pharma, Argentina – for patients treated in Argentina); 3) follow-up of at least 3 months after CBD initiation and sufficient data regarding seizure frequency at baseline.

The following data, extracted from medical records, were collected: demographics, clinical history, genetic data, degree of intellectual disability (ID), seizure types, baseline seizure frequency and previous/concomitant ASMs and presence of a concomitant structural aetiology, defined according to the assessment of the treating clinician.

Baseline seizure frequency was defined as the number of seizures per month during the 3 months preceding CBD initiation, based on information reported in the clinical records. If the exact seizure count was unavailable, clinicians were asked to assign each patient to a category according to the estimated number of seizures per month during the previous 3 months, as follows: daily ( $> 30$  seizures/month), weekly (5–30 seizures/month), monthly (1–4 seizures/month), or yearly ( $< 1$  seizure/month). Patients with  $\geq 20$  seizures per month at baseline were classified as having ‘highly active’ epilepsy, according to previous literature.<sup>14,15,17,18</sup>

Patients with daily seizures were therefore all included in the ‘highly active’ group, whereas patients with monthly and yearly seizures were included in the less active group. Regarding patients with weekly seizures, they were included in the analysis only when the exact number of seizures was available.

All included patients were treated with CBD according to local clinical practice and in accordance with the regulatory framework of the country of enrollment. Patients without a confirmed diagnosis of LGS, DS, or TSC-related epilepsy were operationally classified as receiving CBD off-label.

Outcomes evaluated included mean seizure reduction,  $\geq 50\%$  and  $\geq 75\%$  seizure reduction, and seizure freedom at last follow-up compared to the baseline period, as well as CBD retention at last follow-up and the presence of side effects attributed to CBD during the follow-up period. These outcomes were first evaluated in the overall study cohort and then stratified according to seizure frequency, comparing patients with highly active epilepsy with the patients with less active epilepsy.

As an overall measure of efficacy and tolerability, the Clinical Global Impressions improvement (CGI-I) scale was also employed.<sup>19</sup> The CGI-I is a clinician-rated instrument that assesses the degree of change in the condition of a patient since treatment initiation, using a 7-point Likert scale ranging from 1 (‘very much improved’) to 7 (‘very much worse’).

## 2.1. Statistical analysis

Descriptive statistics were used to summarize the study cohort. Associations between categorical variables were examined with Fisher’s exact test. Continuous variables were compared using either the unpaired *t*-test or the Mann-Whitney *U* test, depending on whether their

distribution was normal or non-normal.

Comparisons of treatment response (mean seizure reduction,  $\geq 50\%$  and  $\geq 75\%$  seizure reduction, and seizure freedom) were performed between patients with and without highly active epilepsy using Mann-Whitney *U* test and Fisher's exact test. A post-hoc sensitivity analysis was conducted to determine the Minimal Detectable Difference (MDD) for the primary efficacy outcomes. The MDD was defined as the smallest absolute difference in proportions between the two groups that could be detected with 80% statistical power at a two-sided significance level of  $\alpha = 0.05$ . Calculations were performed using a standard normal approximation for the difference between two proportions, utilizing the overall pooled sample proportions to estimate variance.

Kaplan–Meier survival curves were generated to evaluate CBD retention between patients with and without highly active epilepsy, using the time from CBD initiation to CBD withdrawal as the event of interest, with follow-up duration truncated at 24-months.

In the overall population, a multivariable logistic regression analysis was performed to identify factors associated with achieving a  $\geq 50\%$  responder rate, adjusting for syndrome category, age at CBD initiation, number of prior ASMs, structural aetiology, intellectual disability degree, and baseline seizure frequency, considered as a dichotomous variable (highly active vs. less active epilepsy).

An additional multivariable analysis was conducted within the subgroup of patients with highly active epilepsy. This model included sex, age at seizure onset, age at CBD initiation, history of febrile seizures, degree of intellectual disability, concomitant structural aetiology, number of ASMs before CBD initiation, CBD dose at last follow-up, prior use of non-pharmacological treatments, and concomitant clobazam therapy, selected a priori as clinically relevant covariates.<sup>7,20–22</sup> Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated.

As a sensitivity analysis, comparisons between patients with highly active epilepsy and the remaining cohort were repeated after stratifying patients according to an alternative threshold of baseline seizure frequency ( $\geq 30$  seizures/month vs  $< 30$  seizures/month).

Statistical analyses were conducted using R Studio version 4.2.3. Test results with  $P < 0.05$  were considered statistically significant.

### 3. Results

#### Baseline characteristics.

A total of 229 patients (116 female, 50.7%) with monogenic DEE were included in the study. The most common aetiologies were SCN1A in 78 (34.1%) patients, followed by TSC2 in 29 (12.7%), CDKL5 in 12 (5.2%), MECP2 in 10 (4.4%), and STXBP1 in 5 (2.2%) (see Supplementary table 1 for a full list of monogenic aetiologies). Median (interquartile range, IQR) age at epilepsy onset was 5 months (IQR: 3–12, range: 0–264). CBD was initiated at median age of 11 years (IQR: 6.2–18.3, range: 0.3–52), with 168 patients (73.4%) starting treatment during childhood or adolescence ( $< 18$  years).

Of the 229 patients, 78 patients (34.1%) were diagnosed with DS, 30 patients (13.1%) with LGS and 29 patients (12.7%) with DEE secondary to TSC (TSC-DEE). The remaining 92 patients (40.2%) did not meet the criteria for any of the above-cited syndromes and were diagnosed with 'other DEE'.

Participants were divided in two groups according to baseline seizure frequency in the 3 months preceding CBD initiation. The group with highly active epilepsy ( $\geq 20$  seizures per month) included 152 patients (66.4%). Baseline demographic and clinical characteristics according to seizure frequency are summarized in Table 1.

At the time of CBD prescription, patients with highly active epilepsy were significantly younger ( $p = 0.014$ ), had more frequently a concomitant structural aetiology ( $p = 0.03$ ), had failed a higher number of ASMs ( $p = 0.04$ ) and were more frequently treated with non-pharmacological interventions ( $p < 0.001$ ), including ketogenic diet, vagus nerve stimulation, and epilepsy surgery. Patients with highly

**Table 1**

Demographic and clinical characteristics of the study cohort according to baseline seizure frequency.

|                                                                    | Patients with non-highly active epilepsy (< 20 seizures/month) (n = 77) | Patients with highly active epilepsy ( $\geq 20$ seizures/month) (n = 152) | p value    |
|--------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------|------------|
| Number of seizures per month, n, median (IQR)                      | 4 (2–8.5)                                                               | 75 (39.5–150)                                                              | $< 0.0001$ |
| Age at epilepsy onset, months, median (IQR)                        | 4 (3–10.5)                                                              | 5 (2–16.8)                                                                 | 0.34       |
| Age at CBD prescription, years, median (IQR)                       | 14 (7.6–21)                                                             | 9.7 (6–17)                                                                 | 0.014      |
| Sex, female, n/N (%)                                               | 33/77 (42.9)                                                            | 83/152 (54.6)                                                              | 0.096      |
| Family history of epilepsy in 1st or 2nd degree relatives, n/N (%) | 17/66 (25.8)                                                            | 31/150 (20.7)                                                              | 0.48       |
| Intellectual disability, n/N (%)                                   |                                                                         |                                                                            | $< 0.001$  |
| Mild                                                               | 9/74 (12.2)                                                             | 3/149 (2.0)                                                                |            |
| Moderate                                                           | 26/74 (35.1)                                                            | 34/149 (22.8)                                                              |            |
| Severe/profound                                                    | 39/74 (52.7)                                                            | 112/149 (75.2)                                                             |            |
| Clinical diagnosis, n/N (%)                                        |                                                                         |                                                                            | $< 0.001$  |
| LGS                                                                | 3/77 (3.9)                                                              | 27/152 (17.8)                                                              |            |
| DS                                                                 | 48/77 (62.3)                                                            | 30/152 (19.7)                                                              |            |
| TSC-related DEE                                                    | 7/77 (9.1)                                                              | 22/152 (14.5)                                                              |            |
| Other DEE                                                          | 19/77 (24.7)                                                            | 73/152 (48.0)                                                              |            |
| Concomitant structural aetiology, n/N (%)                          | 7/66 (10.6)                                                             | 34/148 (23.0)                                                              | 0.039      |
| Previous history of epilepsy surgery, n/N (%)                      | 1/77 (1.3)                                                              | 7/149 (4.7)                                                                | 0.27       |
| History of ketogenic diet, n/N (%)                                 | 13/83 (15.6)                                                            | 66/149 (44.3)                                                              | $< 0.001$  |
| History of vagus nerve stimulation, n/N (%)                        |                                                                         |                                                                            | 0.42       |
| No                                                                 | 64/75 (85.3)                                                            | 120/147 (81.6)                                                             |            |
| Yes, but not active at CBD prescription                            | 5/75 (6.7)                                                              | 7/147 (4.8)                                                                |            |
| Yes, and active at CBD prescription                                | 6/75 (8.0)                                                              | 20/147 (13.6)                                                              |            |
| Number of ASM tried prior to CBD prescription, n, median (IQR)     | 6 (4–7)                                                                 | 7 (4–9)                                                                    | 0.04       |
| CBD dose at last follow-up, median (IQR)                           | 10 (9–15)                                                               | 15 (10–20)                                                                 | $< 0.001$  |

Abbreviations: CBD = cannabidiol; LGS = Lennox-Gastaut syndrome; DS = Dravet syndrome; TSC = Tuberous sclerosis complex; DEE = Developmental and epileptic encephalopathy; ID = intellectual disability; IQR = Interquartile range. Percentages are calculated based on available data.

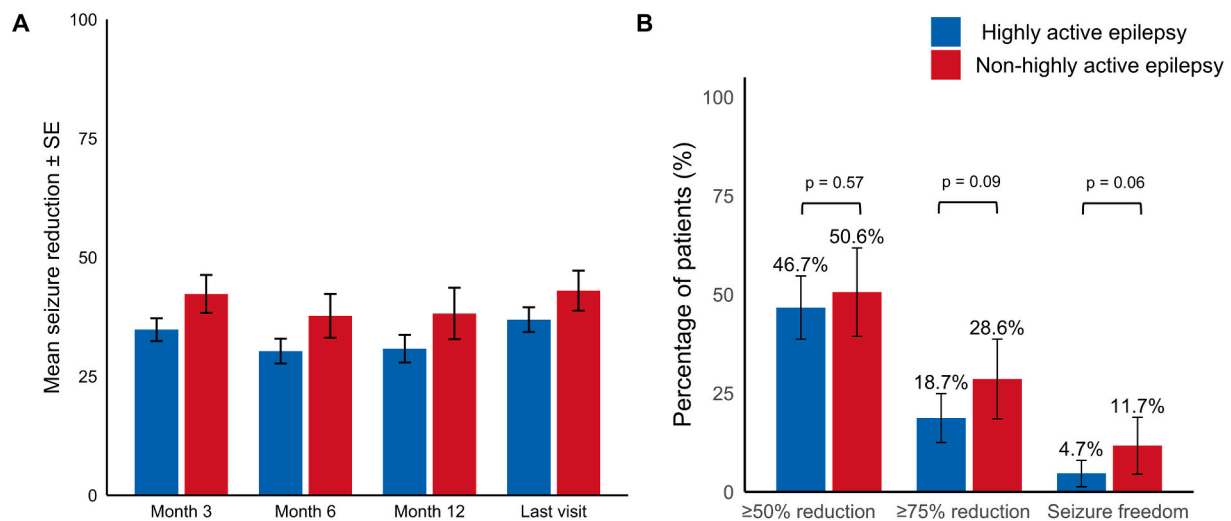
active epilepsy had a significantly higher proportion of off-label prescriptions ( $p < 0.001$ ).

#### Effectiveness of CBD.

Patients received a median CBD dose of 13 mg/kg/day (IQR: 9.9–20) and were followed for a median of 18 months (IQR: 18–27.8). Patients with highly active epilepsy received a significantly higher CBD dose at the last follow-up compared with patients with less active epilepsy, with median values of 15 mg/kg/day (IQR: 10–20) and 10 mg/kg/day (IQR: 9–15), respectively ( $p < 0.001$ ).

Mean seizure reduction over time (months 3, 6, 12, and last visit) is shown in Fig. 1A for patients with and without highly active epilepsy. Across the cohort, the mean seizure reduction at last follow-up was 38.7% (Standard Deviation, SD: 33.7). In the subgroup of patients with highly active epilepsy, mean seizure reduction at last follow-up was lower compared with patients with less active epilepsy, but this difference was not statistically significant [36.9% (SD: 32.1) vs. 43.0% (SD: 36.9),  $p = 0.28$ ].

The  $\geq 50\%$  responder rate,  $\geq 75\%$  responder rate, and seizure freedom rate were lower in patients with highly active epilepsy compared with patients with less active epilepsy. Specifically,  $\geq 50\%$  responder rate was achieved in 70 patients (46.7%, 95% CI 38.7–54.7)



**Fig. 1. Effectiveness of cannabidiol treatment according to baseline seizure frequency.** Panel A shows the mean percentage reduction in seizure frequency from baseline to last follow-up in patients with highly active epilepsy ( $\geq 20$  seizures/month) and non-highly active epilepsy ( $<20$  seizures/month). Error bars indicate standard errors. Panel B presents the proportions in each group achieving  $\geq 50\%$  seizure reduction,  $\geq 75\%$  seizure reduction, and seizure freedom at last follow-up.

with highly active epilepsy and in 39 patients (50.6%, 95% CI 39.4–61.8) with less active epilepsy ( $p = 0.58$ ).

Furthermore,  $\geq 75\%$  responder rate was obtained in 28 (18.7%, 95% CI 12.5–24.9%) patients with highly active epilepsy and 22 (28.6%, 95% CI 18.5–38.7%) patients with less active epilepsy ( $p = 0.09$ ). Seizure freedom was observed in 7 patients (4.7%, 95% CI 1.3–8.0%) with highly active epilepsy and in 9 (11.7%, 95% CI 4.5–18.9%) of those with less active epilepsy ( $p = 0.06$ ). These findings are shown in Fig. 1B. Effectiveness outcomes stratified by syndrome category are shown in Supplementary Table 2. Post-hoc MDD calculations indicated that, given the available sample size, the study had 80% power to detect absolute differences of approximately 19.6% for  $\geq 50\%$  response, 16.3% for  $\geq 75\%$  response, and 10% for seizure freedom.

A multivariable analysis showed no significant association between baseline seizure frequency and achieving a  $\geq 50\%$  responder rate (aOR = 0.68, 95% CI: 0.32–1.43;  $p = 0.31$ ), after adjusting for potential confounders, including syndrome category, age at CBD initiation, number of prior ASMs, structural aetiology, and degree of intellectual disability. The only factor associated with a higher likelihood of achieving a  $\geq 50\%$  responder rate was the presence of a concomitant structural aetiology (aOR = 4.37, 95% CI: 1.42–13.49;  $p = 0.01$ ). The full results of the model are reported in Supplementary Table 3.

This finding was then confirmed in patients with highly active epilepsy. In this subgroup, an additional multivariable model identified the presence of a concomitant structural aetiology as the only factor

associated with a higher likelihood of achieving  $\geq 50\%$  seizure reduction (aOR = 3.04, 95% CI: 1.08–8.53;  $p = 0.035$ ). No associations were found between  $\geq 50\%$ -responder rate and sex, history of febrile seizures, degree of ID, number of ASMs prior to CBD initiation, CBD dose at last follow-up, or concomitant clobazam use. The complete results of this analysis are reported in Table 2.

Among patients with highly active epilepsy and a concomitant structural aetiology ( $n = 34$ ), no significant differences emerged between TSC ( $n = 20$ , 19 TSC2 and 1 TSC1) and non-TSC ( $n = 14$ ) patients in terms of  $\geq 50\%$  seizure reduction,  $\geq 75\%$  seizure reduction, seizure freedom, or CGI-I ( $p < 0.1$  for all comparisons). Among non-TSC patients, most common aetiologies were *PAFAH1B1* in 4 patients, and *DYNC1H1* in 2 patients.

Finally, no differences in effectiveness outcomes were observed between patients receiving CBD off-label and those treated on-label, either in the overall population or in the highly active epilepsy subgroup, (all  $p$  values  $> 0.2$ , see Supplementary Table 4 for the complete findings).

#### Safety and tolerability.

At the last follow-up, CBD treatment was ongoing in 190 of 229 patients (83.7%), with comparable rates between patients with highly active epilepsy and patients with less active epilepsy (85.3% vs. 80.5%,  $p = 0.353$ ), as illustrated in Fig. 2A.

Side effects considered related to CBD during the follow-up period were reported in 89 of 229 patients (38.9%). There was no significant difference in the incidence of side effects between patients with highly active epilepsy and the patients with less active epilepsy (37.6% vs. 42.9% respectively,  $p = 0.47$ ).

The most frequently reported side effect was sedation/somnolence (49 of 229, 21.4%), followed by gastrointestinal disturbances (28 of 229, 12.2%), behavioral disturbances (15 of 229, 6.6%), and hepatic toxicity (13 of 229, 5.7%). Notably, both in the overall population and in patients with highly active epilepsy, off-label prescription was not associated with a higher incidence of side effects (all  $p$  values  $> 0.2$ , see Supplementary Table 4 for the complete findings).

CGI-I indicated clinical improvement in 131/193 (67.9%) patients, with no difference between patients with highly active epilepsy and the patients with less active epilepsy (70% vs. 63.5% respectively,  $p = 0.41$ ), (see Fig. 2B for a detailed representation of CGI-I scores in the two patient cohorts).

#### Sensitivity analysis.

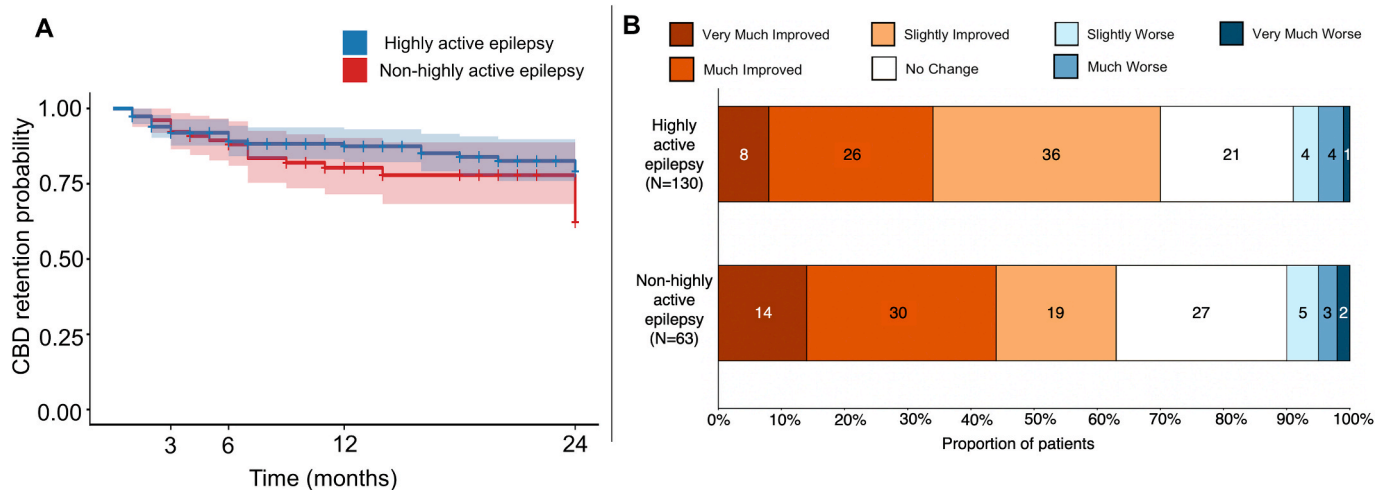
When comparing patients according to a higher cut-off of baseline seizure frequency ( $\geq 30$  seizures/month), similar rates of mean seizure

**Table 2**

Multivariable logistic regression analysis of variables associated with  $\geq 50\%$ -responder rate among patients with highly active epilepsy.

| Variable                                                  | aOR  | 95% CI for aOR | P-value |
|-----------------------------------------------------------|------|----------------|---------|
| Structural etiology                                       | 3.04 | 1.08 – 8.53    | 0.035   |
| Female sex                                                | 1.69 | 0.75 – 3.84    | 0.21    |
| History of febrile seizures                               | 1.36 | 0.43 – 4.31    | 0.61    |
| Concomitant clobazam use                                  | 1.30 | 0.58 – 2.91    | 0.52    |
| Severe/profound intellectual disability                   | 0.88 | 0.33 – 2.37    | 0.80    |
| Use of surgery, ketogenic diet or vagus nerve stimulation | 1.41 | 0.76 – 2.64    | 0.28    |
| Age at seizure onset (months)                             | 1.01 | 1.00 – 1.03    | 0.11    |
| Age at CBD prescription (years)                           | 1.00 | 0.95 – 1.04    | 0.85    |
| Number of prior ASMs                                      | 0.90 | 0.78 – 1.03    | 0.12    |
| CBD dose at last follow-up (mg/kg/day)                    | 1.02 | 0.96 – 1.07    | 0.61    |

Abbreviations: ASM = anti-seizure medications; aOR = adjusted Odds Ratio; CI = Confidence Interval; CBD = cannabidiol.



**Fig. 2. Retention and global clinical impression of CBD treatment according to baseline seizure frequency.** Panel A shows Kaplan–Meier estimates of CBD treatment retention in patients with highly active epilepsy ( $\geq 20$  seizures/month) and non-highly active epilepsy ( $< 20$  seizures/month). Shaded areas indicate 95% confidence intervals. Group differences were assessed using the log-rank test. Panel B shows the distribution of Clinical Global Impressions–Improvement (CGI-I) scores at last follow-up in the two groups.

reduction were observed, although values were numerically lower in patients with highly active epilepsy compared with those with less active epilepsy [35.5% (SD 31.4) vs 43.6% (SD 36.6),  $p = 0.12$ ]. Likewise, the  $\geq 50\%$  responder rate was comparable between groups, being achieved in 65 patients (46.1%, 95% CI 37.9–54.3) with  $\geq 30$  seizures/month and in 44 patients (51.2%, 95% CI 40.6–61.7) with  $< 30$  seizures/month ( $p = 0.50$ ).

Conversely, differences were more pronounced for higher response thresholds. The  $\geq 75\%$  responder rate was achieved in 25 patients (17.7%, 95% CI 11.4–24.0) with  $\geq 30$  seizures/month and in 25 patients (29.1%, 95% CI 19.5–38.7) with  $< 30$  seizures/month ( $p = 0.049$ ). Similarly, seizure freedom was observed in 6 patients (4.3%, 95% CI 0.9–7.6) with  $\geq 30$  seizures/month and in 10 patients (11.6%, 95% CI 4.8–18.4) with  $< 30$  seizures/month ( $p = 0.06$ ).

Regarding safety, CBD retention was similar between patients  $\geq 30$  seizures/month and the remaining cohort (84% vs. 77.9%,  $p = 0.1$ ), and no differences were observed in the incidence of side effects between the two groups (36.4% vs. 44.2%,  $p = 0.26$ ).

#### 4. Discussion

This real-world retrospective study evaluated the effectiveness and tolerability of highly purified CBD in patients with monogenic DEEs and highly active epilepsy, defined as the occurrence of more than 20 seizures per month. Our findings suggest that, even in this severely affected subgroup, CBD may provide a moderate beneficial effect on seizure control, although lower rates of  $\geq 75\%$  responder rate and seizure freedom were observed in the highly active group. Within this group, a concomitant structural aetiology was the only factor associated with a higher likelihood of achieving  $\geq 50\%$  seizure reduction, suggesting that CBD may be particularly relevant in this subgroup of patients.

Compared with patients with less active epilepsy, those with highly active epilepsy had previously failed a greater number of ASMs and were more likely to have received higher doses of highly purified CBD and non-pharmacological treatments, including epilepsy surgery, vagus nerve stimulation, and the ketogenic diet.

These features indicate that the  $\geq 20$  seizures per month subgroup included patients with particularly severe, treatment-resistant epilepsy, characterized not only by high seizure frequency but also by failure of most available therapeutic options for seizure control. In addition, patients with highly active epilepsy more often received CBD off-label, suggesting that clinicians tend to use CBD beyond approved

indications in the most severely affected DEEs.<sup>23</sup>

Despite this greater disease severity, higher seizure burden, more difficult-to-treat epilepsy, and higher prevalence of off-label prescriptions, the primary effectiveness outcomes revealed no significant differences between patients with highly active and less active epilepsy. In the highly active group, mean seizure reduction and  $\geq 50\%$  responder rates were slightly lower but overall comparable to those in patients with less active epilepsy, indicating a similar likelihood of achieving at least moderate treatment response. Consistent results were obtained in the multivariable analysis performed in the overall population after adjusting for baseline seizure frequency and disease severity, as well as in the sensitivity analysis based on a higher threshold of baseline seizure frequency ( $\geq 30$  seizures/month).

In contrast, numerically lower rates were observed for the  $\geq 75\%$  responder rate and seizure freedom in patients with highly active epilepsy. These differences, although not statistically significant (except for the  $\geq 75\%$  responder rate in one sensitivity analysis), may still be clinically relevant in DEEs and should be interpreted in the context of study power. Indeed, post-hoc MDD calculations indicated that, given the sample size, the study was powered to detect absolute differences of approximately 15% for the  $\geq 75\%$  responder rate and about 10% for seizure freedom. Smaller differences in these outcomes may therefore have remained undetected.

Taken together, these findings suggest that CBD represents a valid therapeutic option for patients with DEEs and highly active epilepsy, providing meaningful seizure reduction even in the most treatment-refractory cases. Complete seizure freedom, however, remained uncommon and likely reflects the intrinsic severity and refractoriness of these conditions.

In the overall population and within the highly active subgroup, multivariable analysis consistently showed that the only factor significantly associated with a higher likelihood of achieving a  $\geq 50\%$  seizure reduction with CBD treatment was the presence of a concomitant structural aetiology, even after adjusting for potential confounding factors related to greater disease severity among participants.

Much of the available evidence regarding CBD effectiveness in the presence of brain MRI abnormalities derives from studies in individuals with TSC,<sup>24</sup> whereas data on other conditions associated with structural aetiologies remain limited and heterogeneous.<sup>25–27</sup> Notably, a recent open-label study of 140 patients with focal epilepsy reported comparable effectiveness in those with TSC and non-TSC aetiologies, with a substantial proportion in both groups exhibiting structural

abnormalities and malformations of cortical development.<sup>28</sup> Conversely, a randomized clinical trial evaluating transdermal CBD in focal epilepsy did not demonstrate its superiority over placebo.<sup>29</sup>

In our cohort, despite the relatively small number of patients with highly active epilepsy and concomitant structural and genetic aetiologies, as well as the heterogeneity of the aetiologies involved, we observed no significant differences in treatment effectiveness or CGI-I between individuals with TSC and those with other genetic and structural aetiologies. We may suggest that these findings, although limited by sample size and by the clinician-based classification of structural aetiology, support the possibility that CBD may be effective in structural epilepsies beyond TSC-associated epilepsy.

Additional support for a potential effect of CBD in epilepsies associated with structural aetiologies arises from preclinical studies showing that its therapeutic action may be partly mediated by the modulation of neuroinflammatory pathways through interactions with multiple molecular targets.<sup>30–32</sup> Indeed, as neuroinflammation is thought to play an important role in ictogenesis across several structural epilepsies, both in preclinical and human models<sup>33–37</sup>, future research efforts should specifically address the contribution of anti-inflammatory mechanisms to CBD effectiveness in these conditions.

Importantly, we did not find an influence of concomitant clobazam use on effectiveness outcomes in patients with DEEs and highly active epilepsy, in line with previous studies.<sup>38,39</sup>

Highly purified CBD was a well-tolerated ASM in our cohort, with a relatively low incidence of side effects, and a similar safety profile in patients with highly active epilepsy and less active epilepsy.

When evaluating CGI-I reports,<sup>19</sup> which capture the overall clinical impression of change and integrate both efficacy and tolerability, no differences emerged between patients with highly active and less active epilepsy, further supporting the benefit of CBD in this clinical scenario.

This study presents several limitations. First, its retrospective design relied on clinical records and on the reports of caregivers or clinicians, without the use of standardized scales to evaluate non-seizure outcomes, potentially introducing recall and reporting bias. Prospective studies including standardized assessments of sleep, cognitive, and behavioral domains would allow a more comprehensive evaluation of the overall effectiveness of CBD in patients with DEE. Second, although the multi-centre nature of the study is a strength, as it allowed the inclusion of a relatively large number of patients with DEEs treated with CBD, it may have led to heterogeneity in data collection and seizure reporting, introducing information bias. In addition, differences in clinical practice may have influenced patient selection and treatment patterns, but this is often the case in real-world studies designed to reflect routine clinical management. Third, the comparison between patients with highly active and less active epilepsy was not based on matching or randomization, so residual confounding cannot be excluded. Finally, the assessment of concomitant structural aetiology as a covariate was based on the treating clinician's judgment, which may have varied across centres when determining the clinical relevance of structural brain abnormalities. In a real-world setting, however, this approach is arguably less biased than considering any reported structural abnormality as relevant, particularly in the absence of raw MRI data, which could have introduced even greater heterogeneity (e.g., inconsistent reporting of subtle focal cortical dysplasia or other mild malformations of cortical development).

Despite these limitations, we believe that our study provides clinicians with valuable information regarding the expected effectiveness and tolerability of CBD in patients with DEEs and highly active epilepsy.

## 5. Conclusion

Our study shows that highly purified CBD may represent a feasible treatment option for patients with DEEs and highly active epilepsy. Although no statistically significant differences were observed compared with patients with lower seizure frequency, numerically lower rates of  $\geq 75\%$  response and seizure freedom were seen in the

highly active group. The presence of a concomitant structural aetiology emerged as the only predictor of increased CBD effectiveness within the highly active group. CBD was generally well tolerated in our cohort, with no difference in side effects incidence between the two groups of patients. Future prospective and controlled studies are needed to confirm the effectiveness of highly purified CBD in DEEs with highly active epilepsy and should ideally incorporate additional clinical outcomes beyond seizure control to better assess the overall impact of this treatment.

**Author contributions:** ECI, AO and AC contributed to the concept and design of the study. ECI and AM contributed to drafting a significant portion of the manuscript and figures. All authors significantly contributed to the acquisition and analysis of the data and critically revised the manuscript for intellectual content.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

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