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Research Paper

A multicenter study on the use of purified cannabidiol for children with treatment-resistant developmental and epileptic encephalopathies

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ABSTRACT

Objective: This descriptive, real-world, multicenter study aimed to evaluate the efficacy, safety, and tolerability of purified cannabidiol (CBD) as an add-on therapy in children with treatment-resistant developmental and epileptic encephalopathies (DEE).

Methods: Children aged 0.5 to 16 years who met the International League against Epilepsy (ILAE) criteria for drug-resistant DEE and were treated with purified CBD at 10 different centers between March 2021 and December 2024 were included.

Results: A total of 551 patients were enrolled. The mean age at CBD initiation was 8.5 years (SD 5 years; range 0.5–18). Median follow-up duration was 22 months (range 13–32). Etiologies were structural in 249 (45 %), genetic in 160 (28.8 %), immune-mediated in five (0.9 %), infectious in three (0.5 %), and unknown in 134 (24.3 %). After 12–32 months of follow-up, 279 patients (50.6 %) had a $>$ 50 % reduction in seizure frequency, including 78 (14.2 %) who became seizure-free. A reduction of $<$ 50 % was observed in 106 (19.1 %), and 34 (6.2 %) experienced no change. Adverse events occurred in 32.7 %, mostly mild and transient, improving with dose adjustments. At the last visit, 389 patients (70.6 %) continued CBD, with 173 (31.4 %) maintaining a $>$ 50 % reduction in seizures and 56 (10.2 %) remaining seizure-free.

Conclusions: This study supports the use of purified CBD as an effective, safe, and well-tolerated treatment option for children with drug-resistant DEEs of diverse etiologies.

Abbreviations: ADHD, Attention deficit hyperactivity disorder; ASD, Autism spectrum disorder; ASMs, Antiseizure medications; CGI-I, Clinical Global Impressions – Improvement; CBD, Cannabidiol; DEE-SWAS, DEE with spike-wave activation in sleep; DEEs, Developmental and epileptic encephalopathies; DS, Dravet syndrome; EEG, Electroencephalography; EIDEE, Early infantile developmental and epileptic encephalopathy; EIMFS, Epilepsy of infancy with migrating focal seizures; EMAtS, Epilepsy with myoclonic atonic seizures; FIRES, Febrile illness-related epilepsy syndrome; IESS, Infantile epileptic spasms syndrome; KDT, Ketogenic dietary therapy; LGS, Lennox-Gastaut syndrome; MSNE, Myoclonic status epilepticus in non-progressive encephalopathy; TSC, Tuberous sclerosis complex; VNS, Vagus nerve stimulation.

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1. Introduction

The developmental and epileptic encephalopathies (DEEs) are a group of severe epilepsy syndromes where the developmental delay is caused both by the epileptic activity and the etiology of the underlying disease [1]. Multiple genes have been identified as a cause of DEEs, in addition to structural, immune-mediated, and infectious etiologies. Associated comorbidities include developmental delay, intellectual disability, behavioral problems including attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), psychiatric conditions such as anxiety and depression, speech impairment, and sleep problems, and various systemic complications, including gastrointestinal, musculoskeletal, respiratory, and cardiac conditions [2,3]. DEEs are also linked to significantly increased mortality [2,3]. Seizures in DEEs are frequently drug-resistant, emphasizing the need for effective treatment options.

Evidence from randomized controlled trials, expanded access programs, and real-world studies has established cannabidiol (CBD) as a viable therapeutic option for treatment-resistant epilepsy, with promising potential for broader benefits.

Epidiolex, a purified oral solution of cannabidiol (CBD), was approved by the U.S. Food and Drug Administration (FDA) in 2018 for the treatment of seizures associated with Lennox–Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients aged two years and older, and in 2020 for tuberous sclerosis complex (TSC) in patients one year and older. In 2019, the European Medicines Agency (EMA) granted marketing authorisation for the drug—marketed in Europe as Epidyolex—as adjunctive therapy with clobazam for LGS and DS in patients aged two years and older, with a subsequent extension of the indication to include TSC.

In Argentina, Convupidiol® (Alef Medical) was approved in 2020 by the National Administration of Drugs, Food and Medical Technology (ANMAT) for the treatment of LGS, DS, and TSC in children over two years of age. The formulation contains a non-synthetic, pharmaceutical-grade cannabidiol active pharmaceutical ingredient (API) with a purity of $\geq$ 99.6 %. Manufacturing is conducted in compliance with Good Manufacturing Practices, certified by a competent European medicines authority.

Initially approved for compassionate use in DS [4–6], LGS [7–9], and TSC [10,11], CBD is now been being used off-label for the care for other DEEs, such as epilepsy with myoclonic atonic seizures (EMAtS) [12,13], infantile epileptic spasms syndrome (IESS) [14], febrile illness-related epilepsy syndrome (FIRES) [15], and Sturge Weber syndrome [13,16], as well as CDKL5 [12], Duplication 15q [12], and *KCNT1* [17] and *SYNGAP1* related DEEs [18]. Recently, a large series of children with monogenic epilepsies treated with CBD has been published [19].

Beyond its role in seizure control, CBD may positively impact comorbidities in children with drug-resistant epilepsy, such as neurocognitive impairment, ADHD, ASD, irritability and disruptive behaviors, improving quality of life [20].

Research has improved our understanding of CBD's safety, effectiveness, pharmacokinetics [21], and mechanisms of action, including genetic factors that may support its role in precision medicine. Its interactions with antiseizure medications (ASMs) [22], as well as its combined use with ketogenic dietary therapy (KDT) [21] and vagus nerve stimulation (VNS) [23], are also being investigated. As a result, CBD is now a well-established treatment option for patients with DEEs that are resistant to both pharmacological and non-pharmacological therapies.

Real-world studies are increasingly recognized as an important contribution to a better understanding of the effectiveness, safety, and tolerability of CBD in everyday practice, outside the controlled settings of clinical trials, helping to inform clinical decision-making. Recently, different real-world studies have been conducted on the use of CBD in various treatment-resistant epilepsy patient populations [19,24–27].

This descriptive, real-world, multicenter study aimed to evaluate the efficacy, safety, and tolerability of purified CBD as an add-on therapy in children with treatment-resistant DEE, contributing to the growing body of evidence supporting the use of CBD in this group of patients.

2. Materials and methods

2.1. Design and study subjects

A retrospective, multicenter, descriptive study was conducted. Children aged 0.5 to 16 years who met the ILAE criteria for drug-resistant DEE seen at 10 participating centers and receiving purified CBD between March 2021 and December 2024 were included.

Data were extracted from the medical records of all patients evaluating demographic characteristics, clinical history, seizure and epilepsy types, electroencephalographic (EEG) findings, previous and concomitant ASMs and non-pharmacological treatments, and laboratory and genetic studies. Laboratory studies included complete blood count, liver and kidney function tests, and concomitant ASM levels, when considered necessary. Seizure frequency was compared at baseline and at the last follow-up visit.

Epilepsy type or syndrome, seizure type, and etiology were defined according to the criteria of the International League against Epilepsy [1,28–30].

All patients received a pharmaceutical-grade, purified CBD oral solution (Convupidiol®, Alef Medical, Argentina; CBD concentration: 100 mg/mL), formulated in sesame oil. Treatment with CBD began with an median initial dose of 3 mg/kg/day (range, 2–5), administered twice daily, and was gradually increased every two weeks until reaching intolerance or a maximum dose of 50 mg/kg/day. CBD was given together with a meal.

EEG recordings during sleep and while awake were periodically performed in all patients. Video-EEG and VIDEO-EEG polygraphy were also performed in 249 (45.2 %) and 200 (36.3 %) patients, respectively. Neuroradiologic studies (computed tomography and magnetic resonance imaging) were done in all patients. In addition, genetic and neurometabolic studies were performed in 249 (45.2 %) and 201 (36.5 %) patients, respectively.

Effectiveness was defined as seizure freedom, a seizure reduction of more than 50 %, a reduction less than 50 %, and no changes in seizures. Safety and tolerability were assessed based on adverse effects documented by parents in the seizure diary, as well as laboratory findings, clinical evaluations, and EEG studies.

The 7-point Clinical Global Impressions – Improvement (CGI-I) scale, which measures severity of psychopathology change from the initiation of treatment, was used by the treating neurologist. Scores range from 1 (very much improved) to 7 (very much worse). The scale is routinely used in children receiving CBD in the participating centers. Additional changes, including seizure duration, verbal and non-verbal communication, sleep, eye contact, social smile, motor abilities, and behavior, were evaluated through parental reports and clinical observations.

2.2. Statistical analysis

The data were collected from the clinical records in each center and recorded in a common data sheet. Median differences were established using the Wilcoxon test for paired categorical variables and the Mann-Whitney test for unrelated samples. Statistical analyses were conducted using SPSS v.21 (SPSS Inc., Chicago, IL, USA). A $p < 0.05$ was considered statistically significant.

The study was approved by the Ethics Committee of Hospital de Pediatría J.P. Garrahan (Res. Nr. 1046) and written informed consent was obtained from parents or caregivers of all children.

3. Results

3.1. General characteristics of the patients

Between March 2021 and December 2024, 551 patients were enrolled in the study; 351 (63.7 %) were male and 200 (36.3 %) female. The mean age at CBD initiation was 8.5 years (standard deviation: 8.5 years (SD 5 years; range, 0.5–18 years). The median follow-up duration until the last visit was 22 months (range: 13–32).

The median age at first seizure was 13 months (range: 1 day to 12 years). By definition, all children had DEEs, including LGS in 191 patients (34.7 %), DS in 48 (8.7 %), IESS in 50 (9.1 %), EMAtS in 45 (8.2 %), TSC in 25 (4.5 %), DEE with spike-wave activation in sleep (DEE-SWAS) in 25 (4.5 %), myoclonic status epilepticus in non-progressive encephalopathy (MSNE) [31] in 21 (3.8 %), early infantile DEE (EIDEE) in 13 (2.4 %), epilepsy of infancy with migrating focal seizures (EIMFS) in six (1.1 %), FIRES in five (0.9 %), and other DEEs in 133 (24.1 %) including 96 (17.4 %) monogenic DEEs. The list of the monogenic epilepsies is shown in Table 1.

The underlying etiology was structural in 249 patients (45 %), including hypoxic–ischemic encephalopathy, malformations of cortical development (lissencephaly, polymicrogyria, heterotopia, hemimegalencephaly, and focal cortical dysplasia), and post-infectious lesions. A genetic cause was identified in 160 patients (28.8 %), including monogenic disorders, and other genetic causes, such as Down syndrome, Angelman syndrome, and Rett syndrome. An infectious etiology was identified in three patients (0.5 %), immune-mediated in five (0.9 %), and the etiology remained unknown in 134 cases (24.3 %). Patients with both structural and genetic causes, such as tuberous sclerosis complex and developmental cortical malformations associated with a monogenetic cause, were categorized as having a structural etiology for practical purposes.

Regarding seizure types, 170 patients (30.9 %) had focal seizures, including focal motor seizures in 105 (19.1 %) and focal non-motor seizures in 65 (11.8 %). Tonic seizures were observed in 203 patients (36.8 %), tonic-clonic in 183 (33.2 %), atonic in 169 (30.7 %), focal to bilateral tonic-clonic seizures in 165 (29.9 %), and myoclonic seizures in 111 (20.1 %). Epileptic spasms were reported in 45 children (8.2 %). Status epilepticus was observed in 148 patients (26.9 %), which was focal in 55 (10.1 %) and generalized in 93 (16.9 %).

Regarding seizure frequency, 338 (61.3 %) patients experienced daily seizures, 137 (29.9 %) weekly seizures, 40 (7.3 %) monthly seizures, and eight (1.5 %) less frequent seizures.

Baseline median monthly seizure frequency was 48 (range: 0–231) for focal and 188 (range: 69–355) for generalized seizures; median monthly total seizure frequency was 236 (range: 19–733).

Before starting CBD, patients had been exposed to a median of 15 different ASMs and were taking a median of six ASMs at the time of initiation (range: 2–5). The most frequently prescribed ASMs at the onset of CBD treatment included valproic acid (85.4 %), levetiracetam (75.5 %), topiramate (69.5 %), and clobazam (61.9 %).

Of the 551 patients, 292 (52.9 %) had received KDT. Among them, 222 (76 %) had discontinued KDT before initiating CBD due to an insufficient therapeutic response, whereas 70 patients (23.9 %) remained on KDT in combination with CBD treatment.

Furthermore, 90 patients (16.3 %) had a VNS implanted before starting CBD, with a median duration of VNS therapy of 9.5 years (range: 5–14 years). Epilepsy surgery was performed in 41 patients (7.4 %).

Table 1
Monogenic epilepsies identified in the patients in our cohort.

Gene	Number of patients
SCN1A	48
WWOX	4
SCN2A	3
SCN8A	3
NEXMIF	3
CDKL5	3
STXBP1	3
SYNGAP	3
PCDH19	3
SMC1A	2
PIGS	2
NEDD4L	2
GRIN2B	2
CHD2	2
KCNQ2	2
MECP2	2
CACNA1A	1
UGDH	1
ATP1A3	1
HECW2	1
NARS1	1
GRIN2D	1
SLC6A1	1
PPT1	1
KCNA1	1

3.2. Effectiveness

After a follow-up period of 12 to 32 months, 279 patients (50.6 %) responded to treatment, defined as a reduction in seizure frequency greater than 50 %; 78 children (14.2 %) were seizure-free, 160 patients had a less than 50 % (19.1 %) seizure reduction, and 34 patients (6.2 %) had no changes in seizure frequency.

When analyzing patients according to epileptic syndrome, a good response to CBD was observed in 103/191 (53.9 %) with LGS, 36/50 (72.0 %) with IESS, 33/45 (73.3 %) with EMAtS, 24/48 (50.0 %) with DS, 19/25 (76.0 %) with DEE-SWAS, 7/13 (53.8 %) with EIDEE, 5/10 (50.0 %) with MSNE, 5/6 (83.3 %) with EIMFS, 3/5 (60.0 %) with FIRES, and 105/133 (78.9 %) with other DEEs.

Of the 78 patients (14.2 %) who were seizure free at the end of the follow-up period, 24 had LGS, 11 had IESS, 10 EMAtS, seven TSC, six had DEE-SWAS, one EIMFS, and 19 other DEEs.

Regarding etiology, 129/248 (52.0 %) of the patients with a structural cause, 122/161 (75.7 %) of those with a genetic cause, 105/134 (78.3 %) with an unknown cause, and 1/5 (20.0 %) with an immune-mediated cause were responders. However, none of the three patients with an infectious etiology were responders.

The mean initial CBD dose was 3 mg/kg/day, which was uptitrated to a median daily dose of 27 mg/kg/day (range: 2–50). For the subgroup of responders median CBD dose at the last visit was 26 mg/kg/day (range: 2–50).

During the study period, changes to concomitant ASMs were made in 65 out of 551 patients (11.8 %). In most cases, these adjustments involved either the tapering or addition of one ASM due to clinical need. Out of 70 patients on KDT, finetuning of the diet was necessary in 15 (21.4 %). VNS parameters were adjusted in 32 of 90 patients (35.6 %). The changes were decided by the treating physician, without a systematic pattern.

CBD treatment was discontinued in 160 patients (29.0 %): in 79 patients (14.3 %) due to lack of therapeutic response, including 19 (3.4 %) who experienced an increase in seizure frequency; in 58 patients (10.5 %) due to drug intolerance; and in 23 (4.2 %) due to poor adherence. Among these, 42 patients (26.3 %) discontinued treatment within the first three months.

Regarding comorbidities, clinical improvement, as assessed by the CGI-I scale, was observed between baseline and the last follow-up visit, with the median score improving from 4 (range: 2–6) to 2 (range: 1–7). Improvement was reported in 352 patients (63.9 %), including 45 (12.8 %) rated as very much improved, 139 (39.4 %) as much improved, and 168 (47.7 %) as minimally improved.

Improvement of quality of life was observed regarding: eye contact in 160 (29.0 %), motor skills in 25 (4.5 %), non-verbal communication

in 85 (15.4 %), decreased seizure duration in 95 (17.2 %), social smile in 77 (14.0 %), improved behavior in 91 (16.5 %), sleep patterns in 89 (16.2 %), and in verbal communication in 60 patients (10.9 %).

3.3. Safety and tolerability

Adverse effects were observed in 32.7 % of the patients. They were mostly mild, transient, and improved following CBD dose adjustments. Drowsiness was the most common side effect, reported in 99 patients (17.9 %). Thirty-six patients who experienced drowsiness (36.4 %) were co-medicated with clobazam. The symptoms improved with lowering of either the clobazam or the CBD dose. Other adverse effects were decreased appetite, irritability or behavioral disturbances, and diarrhea. Less frequent adverse events included nausea, vomiting, mood alterations, insomnia, blurred vision, dry mouth, fever, weight loss, and increased seizure frequency. Liver function tests, performed in 389 cases (70.6 %), showed no clinically relevant elevation of liver enzymes, defined as three times the upper limit of normal. In addition, no clinical signs of liver involvement were seen.

3.4. Follow-up

At the last follow-up visit, 389 patients of 551 continued on CBD; 173 (31.4 %) showed a good response to treatment with a seizure reduction of more than 50 %. Fifty-six children (10.2 %) were seizure-free, 120 patients (21.7 %) experienced a seizure reduction of less than 50 %, and 40 patients (7.2 %) showed no change or seizure increase.

In responders, ASMs could be reduced or discontinued in 163 patients (70.2 %), with a median of two ASMs (range: 1–4) remaining at the last follow-up visit.

Table 2 lists the demographic and electroclinical characteristics as well as data on treatment and adverse effects in our cohort of 551 patients with drug-resistant epilepsy treated with purified CBD, while Table 3 shows response to CBD treatment according to seizure types, epilepsy syndromes, and etiologies as well as data at the last follow-up.

4. Discussion

In this retrospective multicenter study, we evaluated the efficacy and tolerability of CBD in a cohort of 551 children with DEEs, including a large subset with genetically confirmed monogenic DEEs. All patients were resistant to treatment, with a high seizure burden and receiving a median of six concomitant ASMs. After a follow-up period ranging from 12 to 32 months, 50 % of patients achieved a greater than 50 % reduction in seizure frequency, and 14.2 % became seizure-free.

Consistent with findings from previous studies [19,24,25], our analysis did not show significant differences in treatment response among different epileptic syndromes or underlying etiologies, supporting a broad effectiveness of CBD across a wide spectrum of childhood drug-resistant epilepsies.

A good response was found in DS, LGS, and TSC, the DEEs for which CDB is approved, but also in other DEEs, such as EMAtS, IESS, DEE-SWAS, MSNE, EIDEE, EIMFS, and FIRES that are currently treated off-label. Similar results have been reported in previous studies [19,24,25]. Additionally, an analysis of a web-based database comprising de-identified electronic health records from over 110 million individuals in the United States identified 4,214 patients treated with purified CBD in 2022, of whom 40 % did not have an indication that was approved by the Food and Drug Administration (i.e., DS, LGS, or TSC) [32]. These findings emphasize the growing real-world use of CBD beyond its current regulatory indications and underscore the need to expand its formal approval to include a broader spectrum of epilepsies, including monogenic epilepsies.

In our study, children were treated with relatively high doses of CBD, up to 50 mg/kg/day. In cases where the initial response was absent or suboptimal, the dose was increased. This approach is supported by

Table 2
Demographic and electroclinical characteristics and data on treatment and adverse effects in a cohort of 551 patients with drug-resistant epilepsy treated with purified cannabidiol.

Patients demographics		Number of patients (%) 551
Sex	Female	200 (36.4 %)
	Male	351 (63.7 %)
Age	At epilepsy onset	13 months (range, 1 day – 12 years)
	At CBD initiation	8.5 years (SD 5 years; range, 0.5–16 years)
Family history of epilepsy	First generation	54 (9.8 %)
Etiology	Structural	249 (45 %)
	Genetic	160 (28.8 %)
	Unknown	134 (24.3 %)
	Immune-mediated	5 (0.9 %)
	Infectious	3 (0.47 %)
Epilepsy and epilepsy syndromes	Lennox-Gastaut syndrome	191 (34.7 %)
	Dravet syndrome	48 (8.7 %)
	Epilepsy with myoclonic atonic seizures	45 (8.2 %)
	Infantile epileptic spasms syndrome	50 (9.1 %)
	DEE-SWAS	25 (4.5 %)
	Epilepsy of infancy with migrating focal seizures	6 (1.1 %)
	Tuberous sclerosis complex	25 (4.5 %)
	Early infantile DEE	13 (2.4 %)
	Myoclonic status epilepticus in non-progressive encephalopathy	21 (3.4 %)
	Febrile infection-related epilepsy syndrome (FIRES)	5 (0.9 %)
	Other DEE	133 (24.1 %)
Type of seizures	Motor focal	105 (19.1 %)
	Non-motor focal	65 (11.8 %)
	Tonic	203 (36.8 %)
	Tonic-clonic	183 (33.2 %)
	Atonic	169 (30.7 %)
	focal to bilateral tonic-clonic	165 (29.9 %)
	Myoclonic	111 (20.1 %)
	Epileptic spasms	45 (8.2 %)
	Focal status epilepticus	55 (10.1 %)
	Generalized status epilepticus	93 (16.9 %)
EEG abnormalities	Focal	75 (13.6 %)
	Generalized	175 (31.8 %
	Focal and generalized	301 (54.6 %)
CBD dose mg/kg/day	Start dose	3 mg/kg/day
	End dose	26 mg/kg/day (range: 2–50)
Co– treatments	Number of ASMs at CBD initiation	6 (range, 2–5)
	Number of ASMs at last follow-up	3 (range, 2–4)
	Ketogenic dietary therapy	70 (12.7 %)
	Vagus nerve stimulation	90 (16.3 %)
	Surgery	41 (7.4 %)
Adverse effects	Drowsiness	99 (17.9 %)
	Loss of appetite	10 (1.8 %)
	Irritability or behavioral problems	13 (2.6 %)
	Diarrhea	8 (1.6 %)
	Weight loss	6 (1.1 %)
	Nausea	16 (2.9 %)
	Vomiting	6 (1.1 %)
	Mood changes	14 (2.5 %)
	Insomnia	3 (0.5 %)
	Blurred vision	2 (0.4 %)
	Dry mouth	1 (0.2 %)
	Fever	2 (0.4 %)
Effectiveness	Seizure freedom	78 (14.2 %)
	Seizure reduction > 50 %	269 (81 %)
	Seizure reduction < 50 %	160 (29.0 %)
	No change	41 (7.4 %)
	Seizure increase	81 (14.7 %)

(continued on next page)

Table 2 (*continued*)

Patients demographics		Number of patients (%) 551
Improvement in comorbidities	Eye contact	160 (29.0 %)
	Motor skills	25 (4.5 %)
	Non-verbal communication	85 (15.4 %)
	Seizure duration	95 (17.2 %)
	Social smile	77 (14.0 %)
	Behavior	91(16.5 %)
	sleep patterns	89 (16.2 %)
	verbal communication	60 (10.9 %)
Follow-up	Median time of follow-up	22 months (range, 13–32)
	Last visit	
Median age	At last follow-up	10.1 (1.6–17.2) years

findings from Szaflarski et al. [33] and Kühne et al. [24], who reported significantly greater efficacy in patients receiving higher CBD doses. Based on these observations, we suggest that dose escalation should be considered in patients who do not respond adequately to lower doses.

The youngest patient in our cohort was 6 months old, therefore CBD treatment was initiated at an earlier age than the currently recommended minimum of one year. Given that many DEEs begin in infancy, earlier initiation of CBD may help mitigate the progressive neurological deterioration often observed in these patients. Kühne et al. [24] reported initiating treatment as early as two months of age. These findings suggest that earlier treatment onset should be considered, particularly in severe early-onset DEEs.

Among the potential mechanisms of action, CBD has been shown to be active in different cellular and physiological processes, such as inflammation, and enhances the concentration of adenosine and GABA, reducing hyperexcitability and neurotransmission. An effect of CBD on ion channels (calcium, potassium, and sodium channels) has also been found [34].

Cerulli Irelli et al. [19], in a large study on monogenic epilepsies, reported favorable responses to CBD in variants associated with structural lesions such as cortical tubers and focal cortical dysplasia, where neuroinflammation has been suggested to play a role. These anti-inflammatory properties of CBD were also considered to be related to the good response they observed in all three patients with DEE-SWAS, consistent with findings by Ferrara et al. [35] and our previous study using enriched CBD [36]. In relation to potential calcium-related mechanisms underlying the efficacy of CBD in epilepsy, all three patients in their series with pathogenic calcium channel variants showed a favourable response to treatment. On the other hand, they found poor responses in patients with GABAergic mutations, while all three with SYNGAP1 variants, associated with glutamatergic signaling, showed optimal seizure control.

In our study, in children with monogenic DEEs, *SCN1A* variants were the most common, together with other sodium channelopathies as well as *SYNGAP1* variants. We found that these patients, as well as those with mutations in *CDKL5*, *MECP2*, and *PCDH19*, demonstrated a favorable response to treatment, both in terms of seizure control and observed behavioral improvements.

Altogether, these findings suggest a role for precision medicine in the use of CBD for different epilepsy syndromes and etiologies.

In our cohort, 29 % of patients discontinued CBD treatment, of whom 33.3 % discontinued within the first three months. Among those who discontinued at a later stage, the primary reason was a loss of efficacy, including in some cases where an initial positive response had been observed. This pattern suggests the development of tolerance in some patients (125/551; 22.7 %). While several studies have reported sustained long-term efficacy of CBD in drug-resistant epilepsy without evidence of tolerance [10,25,34], other real-world investigations have found a potential decline in efficacy over time [24]. These findings show the importance of large sample sizes and long-term follow-ups evaluating the treatment with CBD of children with treatment-resistant epilepsy.

In our series, 63.9 % of patients showed improvement on the CGI-I

Table 3
Efficacy according to etiology, epileptic syndrome, and type of seizure.

		Number of patients	Seizure free	> 50 % seizure reduction	< 50 % seizure reduction	No changes
Etiology	Structural	248	28 (11.2 %)	101 (40.7 %)	87 (35.0 %)	32 (12.9 %)
	Genetic	161	26 (16.1 %)	96 (59.6 %)	39 (24.2 %)	–
	Unknown	134	24 (17.9 %)	81 (60.4 %)	29 (21.6 %)	–
	Immune	5	–	1 (20.0 %)	4 (80.0 %)	–
	Infectious	3	–	–	1 (33.3 %)	2 (66.6 %)
Epilepsy and epilepsy syndromes	Lennox-Gastaut syndrome	191	24 (12.6 %)	79 (41.4)	80 (41.9 %)	8 (4.2 %)
	Dravet syndrome	48	–	24 (50.0 %)	22 (45.8 %)	2 (4.2 %)
	Tuberous sclerosis complex	25	7 (28.0 %)	10 (40.0 %)	7 (28.0 %)	1 (4.0 %)
	Epilepsy with myoclonic atonic seizures	45	10 (22.2 %)	23 (51.1 %)	9 (20.0 %)	3 (6.7 %)
	Infantile epileptic spasms syndrome	50	11 (22.0 %)	25 (50.0 %)	9 (18.0 %)	5 (10.0 %)
	DEE-SWAS	25	6 (24.0 %)	13 (52.0 %)	5 (20.0 %)	1 (4.0 %)
	Epilepsy of infancy with migrating focal seizures	6	1 (16.7 %)	4 (66.7 %)	–	1 (16.7 %)
	Early infantile DEE	13	–	7 (53.8 %)	6 (46.2 %)	–
	FIRES	5	–	3 (60.0 %)	2 (40.0 %)	–
	Myoclonic status	10	–	5 (50.0 %)	2 (20.0 %)	3 (30.0 %)
	Other DEE	133	19 (14.3 %)	86 (64.7 %)	18 (13.5 %)	10 (7.5 %)
Type of seizures	Generalized	381	36 (9.4 %)	180 (47.2 %)	160 (42.0 %)	41 (10.8 %)
	Focal	170	4 (2.4)	85 (50.0 %)	60 (35.3 %)	30 (17.6 %)
	Focal to bilateral tonic-clonic seizure	130	–	76 (58.5 %)	52 (40.0 %)	2 (1.5 %)
Last follow-up visit	Continued in the study	389	56 (10.2 %)	173 (31.4 %)	159 (28.9 %)	34 (6.2 %)

scale between baseline and the last follow-up visit. These findings are in line with previous studies suggesting that CBD, beyond its antiseizure effects, may positively impact quality of life, behavior, cognitive function, motor skills, sleep, and mood [20,24,37,38]. Most patients who experienced a reduction in seizure frequency also showed improvements in associated comorbidities. However, even among those without a decrease in seizure frequency, caregivers often reported clinical improvements.

Although the CGI-I is a simple, subjective, parent-reported measure, it has been suggested that in DEEs, where multiple comorbidities and high levels of parental stress are common [38], greater emphasis should be placed on patient-centered outcome measures. In these cases, comorbidities may have a greater impact on quality of life than the actual seizure burden, underscoring the importance of incorporating the perspectives of patients and caregivers and focusing on the issues most relevant to them [3].

In our group, we recently evaluated the use of purified CBD in children with severe, treatment-resistant ASD without epilepsy and found that these patients may benefit from improvements in some core symptoms of ASD, including repetitive behaviors and social interaction. Additionally, parents reported a perceived improvement in their quality of life [39]. Given the bidirectional relationship between epilepsy and ASD, as children with epilepsy may develop autism, and vice versa, and the potential shared physiological mechanisms, the use of CBD in these patient populations is a promising and challenging area for further investigation.

In our cohort, all patients were instructed to take CBD with meals, and 70 patients (23.9 %) received CBD in combination with a KDT. The CBD formulation used was free of sucralose, making it compatible with ketogenic regimens. These observations are in line with findings from a recent pharmacokinetic study, which demonstrated that co-administration of CBD with food or KDT significantly increases plasma concentrations, potentially enhancing therapeutic efficacy while allowing for lower doses, thus reducing side effects and treatment costs [21]. Similarly, Espinosa-Jovel et al. [25] reported a lower incidence of adverse effects, likely related to the lower CBD dosages used.

Additionally, 90 patients (16.3 %) in our cohort had a VNS implanted prior to starting CBD treatment. We did not observe any synergistic effects between CBD and VNS in this subgroup. However, given the limited evidence on the concurrent use of these therapies, further studies are needed to evaluate possible interactions or additive effects.

We did not observe increased efficacy of CBD when co-administered with clobazam. Although 341 patients (61.9 %) received this combination, no synergistic effects, either positive or negative, were noted in terms of seizure control. However, coadministration was associated with drowsiness in 33 patients. Although earlier studies suggested a potential benefit from this combination, a *meta*-analysis of randomized controlled trials found no significant difference in efficacy between patients receiving CBD with clobazam and those receiving CBD with placebo [40]. Therefore, several authors have questioned the continued recommendation of clobazam coadministration, considering that it may no longer be justified [19,24].

Finally, the potential influence of the placebo effect should be acknowledged. In real-world studies, assessments of seizure frequency, quality of life, and behavioral improvements depend in large part on caregiver reports, which may be subject to bias. Nevertheless, placebo responses are probably stronger at treatment onset, while in longer-term studies, such as ours, it is expected that improvements reflect a true therapeutic effect rather than a placebo response.

This study has some limitations, including its retrospective nature which may have introduced recall bias and less control over data quality. As it was a multicenter study, there may have been missing or inconsistent data between sites. In addition, we acknowledge that changes to concomitant treatments during the study period may have introduced a potential confounding factor when interpreting the efficacy of CBD. However, this reflects how treatment plans for patients with DEEs often need to be adjusted over time in real-life clinical practice. Importantly, the majority of patients in our cohort (79.7 %) did not experience changes to their baseline ASM or non-pharmacological regimen. In spite of this confounding factor, our findings remain consistent with efficacy data from controlled trials and other real-world studies.

However, all centers used a similar CBD protocol, which helped to standardize treatment practices.

Although several real-world studies on the use of CBD for treatment-resistant epilepsy have been published [19,24–27], our study adds a large and heterogeneous cohort of children with a broad spectrum of different DEE, including monogenic DEE, which are generally highly resistant to treatment, seen over an extended follow-up period. This allows for a more precise evaluation of the role of CBD in genetic, treatment-resistant DEE and supports its potential application within a precision medicine framework. Furthermore, our cohort included very young children and demonstrated the safe use of high doses of CBD in some cases, contributing meaningful evidence to guide clinical practice. Nevertheless, future prospective studies are needed to assess the role of CBD, not only as a palliative option in severe cases, but also as an earlier intervention in the treatment course of DEEs.

5. Conclusions

The findings of our study support the use of purified CBD as an effective, safe, and well-tolerated treatment option for patients with various types and etiologies of DEEs, including monogenic cases, after long-term follow-up.

A similarly good response was observed between the DEEs for which CBD has been approved (i.e., DS, LGS, and TSC), and other DEEs for which CBD is currently used off-label. These findings highlight the need to approve the use of CBD in a broader range of DEEs that are resistant to pharmacological and non-pharmacological treatments.

High doses were safely administered in our patient cohort to achieve a reduction in seizure frequency. CBD was also used in patients under one year of age, and early initiation of treatment in this group with treatment-resistant DEEs may help mitigate the impact of electroclinical activity on development during this vulnerable period.

In addition to reduced seizure frequency, improvements in CGI-I scores and comorbidities such as verbal and non-verbal communication, seizure duration, behavior, and sleep were observed.

The real-world effectiveness and safety of CBD in these different DEEs suggest underlying mechanisms consistent with a precision medicine approach. Our findings emphasize the need for large, prospective studies to confirm these results and potentially expand therapeutic indications.

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

CRediT authorship contribution statement

Gabriela Reyes Valenzuela: Data curation. **Alberto Espeche:** Conceptualization. **Sebastian Fortini:** Data curation. **Beatriz Gamboni:** Data curation. **Javier Adi:** Data curation. **Marco Semprino:** Data curation. **Lorena Fasulo:** Data curation. **Santiago Galicchio:** Data curation. **Pedro Cachia:** Data curation. **Santiago Chacón:** Data curation. **Agustin Calvo:** Data curation. **Lucas Beltran:** Data curation. **Claudia Bautista:** Data curation. **Roberto H Caraballo:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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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