

Research Paper

Use of purified cannabidiol as add-on therapy in children with non-self-limited focal epilepsies of childhood: A multicenter study

Gabriela Reyes Valenzuela^a, Alberto Espeche^b, Sebastian Fortini^c, Beatriz Gamboni^d, Javier Adi^d, Marco Semprino^e, Lorena Fasulo^e, Santiago Galicchio^f, Pedro Cachia^f, Santiago Chacón^g, Agustín Calvo^h, Lucas Beltránⁱ, Claudia Bautista^j, Viviana Venegas^k, Carolina Alvarez^k, Paula Ivarola^a, Roberto Caraballo^{a,*}

^a Hospital de Pediatría Prof. Dr. Juan P. Garrahan, Buenos Aires, Argentina

^b Hospital Público Materno Infantil, Salta, Argentina

^c Hospital del Niño Jesús, Tucumán, Argentina

^d Hospital Pediátrico Humberto H. Notti, Mendoza, Argentina

^e Clínica San Lucas, Neuquén, Argentina

^f Hospital de Niños Víctor J. Vilela, Rosario, Santa Fe, Argentina

^g Centro Neurología Infantil "CENI" Gualeguaychú, Argentina

^h Hospital Regional de Comodoro Rivadavia, Comodoro Rivadavia, Argentina

ⁱ Hospital de Niños Juan Pablo II, Corrientes, Argentina

^j Hospital San Roque, Paraná, Entre Ríos, Argentina

^k Clínica Alemana, Santiago de Chile, Chile

ARTICLE INFO

Keywords:

Purified cannabidiol
Treatment-resistant epilepsies
Pediatric
Tuberous sclerosis complex
Non-self-limited focal epilepsy

ABSTRACT

Objective: Evidence for purified cannabidiol (CBD) in children with treatment-resistant non-self-limited focal epilepsies (non-SeLFEs) remains limited. We evaluated its long-term effectiveness and tolerability in a multicenter pediatric cohort.

Methods: We retrospectively analyzed 79 children with treatment-resistant non-SeLFEs treated with adjunctive purified CBD at 11 pediatric neurology centers in Argentina and Chile. All had previously received ≥ 4 ASMs. CBD dosing was individualized according to response and tolerability. Outcomes included changes in seizure frequency and interictal EEG abnormalities, and treatment tolerability.

Results: After a mean follow-up of 30 months (range, 6–44), 43/79 patients (54.4 %) achieved a ≥ 50 % reduction in seizure frequency, including four (5.1 %) who became seizure-free. The mean CBD dose was 34 mg/kg/day (range, 10–40). Response remained stable at 12, 18, 24, and 30 months. Responder rates did not differ significantly between patients with TSC and those with non-TSC focal epilepsies. No significant associations were found between response and seizure type, age at seizure onset, epilepsy duration, age at CBD initiation, or concomitant ASMs. Interictal epileptiform abnormalities improved among responders. Adverse events occurred in 23 patients (29.1 %), were predominantly mild and transient, and were generally manageable with dose adjustments; drowsiness was the most common. No serious treatment-related adverse events occurred.

Conclusion: Adjunctive purified CBD was associated with sustained seizure reduction and good long-term tolerability in children with treatment-resistant non-SeLFEs. Responses were observed across different focal epilepsy etiologies, supporting further evaluation of CBD in this population. Individualized dosing according to response and tolerability may be appropriate in this heterogeneous population.

1. Introduction

Focal epilepsies in childhood are a heterogeneous group of disorders

with different etiologies, clinical manifestations, and prognoses. The self-limited focal epilepsies (SeLFEs) represent the paradigmatic group of childhood-onset focal epilepsy syndromes and are generally

* Corresponding author at: Combate de los Pozos 1881., 1245 Buenos Aires, Argentina.

E-mail address: robertohcaraballo@gmail.com (R. Caraballo).

<https://doi.org/10.1016/j.yebeh.2026.111323>

Received 18 August 2026; Received in revised form 18 September 2026; Accepted 25 September 2026

1525-5050/© 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

characterized by spontaneous remission and favorable long-term outcomes. In contrast, non-self-limited focal epilepsies (non-SeLFEs) comprise focal epilepsies that do not spontaneously remit and often require ongoing antiseizure medication (ASM) management, with a substantial proportion becoming treatment-resistant, emphasizing the importance of syndrome identification for prognosis and treatment [1].

Non-SeLFEs may arise from a broad range of etiologies, including structural, genetic, infectious, metabolic, immune-mediated, and unknown causes. Structural etiologies include focal cortical dysplasia, other malformations of cortical development, hemispheric syndromes, neurocutaneous disorders such as tuberous sclerosis complex (TSC) and Sturge–Weber syndrome, and hippocampal sclerosis, while immune-mediated causes include disorders such as Rasmussen encephalitis. Several well-defined focal epilepsy syndromes, such as sleep-related hypermotor epilepsy (SHE), may have genetic, structural, or unknown etiologies. Accurate identification of the seizure type, electroclinical syndrome, and underlying etiology is essential, as management may include etiology-specific interventions such as epilepsy surgery, immunotherapy, dietary therapies, or targeted treatments for inherited metabolic and genetic disorders [2,3].

Despite advances in diagnostic evaluation and therapeutic options, approximately 20–40% of children with focal epilepsies develop treatment-resistant epilepsy [3], highlighting the need for additional effective and well-tolerated treatment strategies. Purified cannabidiol (CBD), a non-psychoactive phytocannabinoid derived from the *Cannabis sativa* plant, has emerged as an important therapeutic option for several DEEs. Randomized controlled trials and long-term open-label extension studies have demonstrated its efficacy and safety as adjunctive therapy in Dravet syndrome, Lennox–Gastaut syndrome, and TSC [4–7], followed by studies in other specific epilepsy syndromes and monogenic epilepsies [8,9].

To date, relatively little has been published on the use of CBD in non-SeLFEs. In an open-label, expanded-access study, CBD significantly reduced focal seizure frequency in patients with treatment-resistant focal epilepsy, including individuals with TSC [10]. In addition, an Argentine study of adults with treatment-resistant focal epilepsy found adjunctive CBD to be effective, safe, and well tolerated, with treatment also associated with significant improvements in quality of life [11]. Other real-world and observational studies have suggested potential benefits of CBD in treatment-resistant focal epilepsies and in heterogeneous cohorts that included patients with focal seizures or focal epilepsy [12,13]. However, these studies did not specifically characterize childhood non-self-limited focal epilepsies as a distinct population. Evidence specifically addressing the effectiveness of CBD in children with well-defined non-SeLFEs therefore remains scarce. Given the substantial burden of drug resistance among children with non-SeLFEs and the favorable efficacy and tolerability profile of purified CBD demonstrated in other pediatric epilepsy syndromes, further evaluation of CBD in this population is needed.

Given the paucity of pediatric data, particularly from real-world settings, the aim of this retrospective, multicenter study was to evaluate the effectiveness and tolerability of adjunctive purified CBD in children with treatment-resistant non-SeLFEs.

2. Material and methods

2.1. Study design and population

We conducted a retrospective, multicenter study of patients with non-SeLFEs treated with adjunctive purified CBD at 11 pediatric neurology departments in Argentina and Chile between December 2022 and May 2026. All consecutive patients meeting the eligibility criteria who initiated CBD during the study period were included in the database.

The following inclusion criteria were applied: (1) normal or abnormal development and cognition before epilepsy onset; (2) epilepsy

onset between 2 and 12 years of age; (3) focal motor or non-motor seizures, with or without consciousness impairment; (4) focal EEG abnormalities, with or without associated generalized abnormalities; and (5) focal to bilateral tonic-clonic seizures, when present. Seizure types, epilepsy syndromes, and etiologies were classified according to the most recent International League Against Epilepsy (ILAE) criteria [1,14].

Although the efficacy of CBD in children with TSC has been established in a randomized, placebo-controlled clinical trial [7] and subsequent open-label extension study [15], patients with TSC were included in the present cohort to allow comparison of treatment response between TSC-associated focal epilepsy and treatment-resistant focal epilepsies of other etiologies, as previously explored by Patel et al. [10].

In the patients with a focal structural etiology surgical treatment was considered; however, this option was ruled out in all of them. Therefore, pure forms of non-SeLFE were included. Patients with focal epilepsy in the context of developmental and epileptic encephalopathies (DEE) were excluded, as were patients with SeLFE, familial focal epilepsies in childhood, focal seizures in generalized epilepsies or epileptic encephalopathies, and progressive neurological or systemic disease [1].

2.2. Clinical and EEG assessment

Demographic and clinical data were extracted from the medical records at each participating center using a standardized data collection form. Variables included age and sex, developmental history, age at epilepsy onset, seizure and epilepsy types, etiology, EEG findings, previous and concomitant ASMs, previous and concomitant non-pharmacological treatments, neuroimaging, laboratory findings, and genetic studies.

Parents and/or caregivers maintained seizure diaries documenting seizures occurring at home and school. At each follow-up visit, seizure frequency, type, and duration were reviewed by the treating neurologist. Seizure frequency during the 3 months preceding CBD initiation was considered the baseline and was compared with seizure frequency at the last follow-up visit.

All patients underwent serial EEG and/or video-EEG recordings, including recordings of at least 2 hours, which were evaluated by the treating neurologists. Interictal EEG abnormalities were quantitatively assessed before and after CBD initiation. EEG improvement was defined as a $\geq 50\%$ reduction in interictal focal epileptiform discharges during wakefulness and/or sleep.

Brain magnetic resonance imaging (MRI) was performed in all patients, and 22 patients also underwent computed tomography (CT). Genetic testing, including epilepsy gene panels and/or exome sequencing, was performed when clinically indicated. Laboratory monitoring included serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and kidney function tests before CBD initiation and during follow-up. Serum concentrations of concomitant ASMs were measured when clinically indicated but were not systematically assessed in all patients. Available data on school performance and neuropsychological assessments, including the Terman–Merrill and Wechsler Intelligence Scale for Children (WISC III or IV), were also collected.

2.3. Cannabidiol treatment

All patients received a pharmaceutical-grade purified CBD oral solution (Convupidiol®, Alef Medical, Argentina; CBD concentration, 100 mg/mL) formulated in sesame oil. CBD was initiated at a median dose of 3 mg/kg/day (range, 2–5 mg/kg/day), administered in two divided doses, and gradually titrated every 2 weeks according to clinical response and tolerability, up to a maximum dose of 40 mg/kg. Dose adjustments were individualized according to seizure response, EEG findings, and tolerability. Whenever clinically feasible, changes in concomitant ASMs and non-pharmacological treatments were kept to a minimum after CBD initiation.

2.4. Outcomes

The primary effectiveness outcome was the change in seizure frequency from baseline to the last follow-up visit. Treatment response was categorized as seizure freedom, 50–99% reduction in seizure frequency, < 50% reduction, or worsening of seizure frequency.

Secondary outcomes included changes in interictal EEG abnormalities and treatment tolerability. Safety and tolerability were assessed based on adverse events reported by parents day. Patients were advised to take CBD with a meal; however, administration in relation to food was not systematically documented.

or caregivers and documented in seizure diaries or medical records, together with findings from clinical evaluations and laboratory monitoring.

2.5. Statistical analysis

Data from each participating center were entered into a standardized database. Continuous variables were summarized as mean and standard deviation or median and range, as appropriate, and categorical variables as frequencies and percentages. Paired continuous variables were compared using the Wilcoxon signed-rank test, whereas comparisons between independent groups were performed using the Mann–Whitney U test. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Statistical analyses were performed using SPSS version 21 (SPSS Inc., Chicago, IL, USA). A two-sided *p* value < 0.05 was considered statistically significant.

2.6. Ethical considerations

The study was approved by the Ethics Committee of the principal investigator's institution (Resolution No. 1046). Additional approval for participation and data sharing was obtained from the institutional review board of each participating center. Written informed consent was obtained from the parents or legal guardians of all participants.

3. Results

3.1. Patient characteristics and treatment

A total of 79 patients with non-SeLFEs were included. Fifty (63.3%) were male and 29 (36.7%) were female. Patient age ranged from 3 to 16 years, with a mean age of 9 years and a median age of 10 years. The median age at CBD initiation was 9 years (range, 4–12 years). Four patients had a history of febrile seizures and seven had a family history of epilepsy.

The etiology was structural in 49 patients (62.0%) and unknown in 30 (38.0%). Among patients with a structural etiology, focal cortical dysplasia was identified in 15, TSC in 13, prenatal vascular injury in seven, sequelae of perinatal injury in six, polymicrogyria in five, and Sturge–Weber syndrome in three. Genetic testing was performed in 18 patients and did not identify a causative variant.

All patients had previously received at least four ASMs, with a mean of six ASMs per patient, before CBD initiation. Concomitant ASMs included levetiracetam (70%), valproic acid (55%), lacosamide (49%), oxcarbazepine (40%), lamotrigine (32%), clobazam (31%), carbamazepine (30%), phenobarbital (20%), topiramate (19%), and phenytoin (15%). In addition, 12 patients (15.2%) were receiving ketogenic dietary therapy (KDT), and 12 (15.2%) had undergone vagus nerve stimulation (VNS).

The CBD dose during follow-up ranged from 10 to 40 mg/kg/day, with a mean dose of 34 mg/kg/day.

3.2. Effectiveness

After a mean follow-up of 30 months (range, 6–44 months), 43 of 79

patients (54.4%) achieved a $\geq 50\%$ reduction in seizure frequency, including four patients (5.1%) who became seizure-free. Of the four seizure-free patients, two had TSC and two had epilepsy of unknown etiology. The remaining 36 patients (45.6%) had a < 50% reduction in seizure frequency. The mean time to response was 6 months; range, 5–8 months. Among patients with available follow-up at each time point, treatment response remained stable at 12, 18, 24, and 30 months.

Of the 79 patients, 13 (16.5%) had TSC and 66 (83.5%) had focal epilepsy of other etiologies. Median age was 7.5 years (range, 2–13 years) in the TSC group and 8.5 years (range, 3–14 years) in the non-TSC group. Median CBD doses were similar between the TSC and non-TSC groups (28 and 30 mg/kg/day, respectively). At different follow-up time points, CBD treatment was associated with median reductions from baseline ranging from 49% to 79% in focal seizures and from 43% to 81% in total seizures in the TSC group, compared with 40% to 67% and 41% to 66%, respectively, in the non-TSC group. Responder rates did not differ significantly between the two groups, although the TSC subgroup was small (*n* = 13).

No significant differences in treatment response were observed according to focal seizure type (motor or non-motor, with or without impairment of consciousness) or between patients with focal seizures alone and those with focal to bilateral tonic-clonic seizures. Similarly, responders and non-responders did not differ significantly in age at seizure onset, epilepsy duration, or age at CBD initiation. No specific positive or negative association was identified between treatment response and individual concomitant ASMs.

Among patients receiving concomitant non-pharmacological therapies, three patients receiving KDT and two treated with VNS achieved a $\geq 50\%$ reduction in seizure frequency after CBD initiation.

Comparison of EEG findings before and after CBD initiation showed improvement in focal epileptiform abnormalities and bilateral discharges among patients who achieved a $\geq 50\%$ reduction in seizure frequency. Improvement in interictal EEG abnormalities was associated with greater seizure reduction (Figs. 1 and 2).

3.3. Safety and tolerability

Adverse effects were reported in 23 patients (29.1%). Drowsiness was the most common adverse effect, occurring in 10 patients; five of these patients were receiving concomitant clobazam. Drowsiness improved after reduction of the clobazam and/or CBD dose. Other adverse effects included decreased appetite, irritability or behavioral disturbances, diarrhea, nausea, vomiting, insomnia, dry mouth, blurred vision, and fever. Adverse effects were predominantly mild and transient and generally improved following CBD dose adjustment. No increase in seizure frequency was observed after CBD initiation. No elevations in serum transaminases or clinical evidence of liver disease were observed during follow-up, including among patients receiving concomitant valproate, and no patient discontinued CBD because of hepatotoxicity. Adverse effects are summarized in Table 1.

3.4. Long-term outcomes

At 30 months, 60 patients remained on CBD treatment. Among patients who discontinued CBD before 30 months, the reason was insufficient seizure response. However, some patients with a < 50% reduction in seizure frequency continued treatment because caregivers and treating physicians reported improvements in cognitive and/or behavioral functioning and quality of life. Across the entire cohort, 43 patients maintained a $\geq 50\%$ reduction in seizure frequency at their last assessment, including four who remained seizure-free (see Table 2).

Among 43 patients with a favorable long-term response, 27 experienced only sporadic seizures and reported improvement in quality of life, without requiring the addition or modification of concomitant ASMs, KDT, or VNS. Seven patients required adjustments to concomitant ASMs, while in two additional patients, sulthiame and brivaracetam,

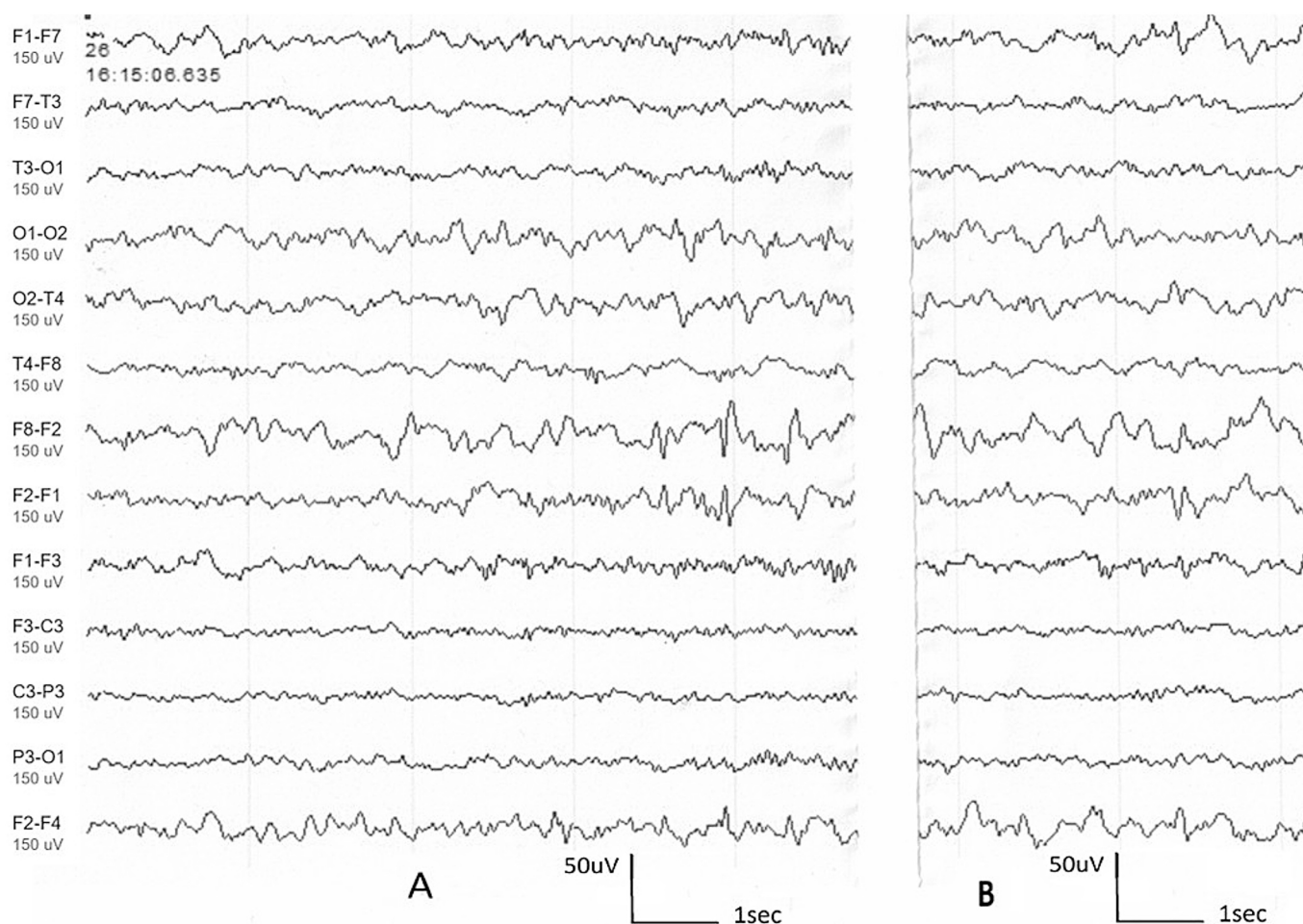


Fig. 1. EEG recordings from an 8-year-old boy with treatment-resistant focal epilepsy secondary to unilateral polymicrogyria. (A) Sleep EEG before CBD initiation showing focal spikes over the right frontal region. (B) Sleep EEG obtained 6 months after CBD initiation, when the patient had become seizure-free, showing resolution of the epileptiform abnormalities.

respectively, were added without further improvement in seizure control (9/79, 11.4%).

Neuropsychological assessments were not performed systematically. Nevertheless, based on parent/caregiver reports, clinical impressions of the treating neurologists, school performance, and available formal neuropsychological assessments ($n = 14$), cognitive and/or behavioral improvement was reported in 30/43 patients with a favorable response after a mean follow-up of 30 months.

4. Discussion

In this retrospective, multicenter real-world study, adjunctive purified CBD was associated with sustained seizure reduction and good tolerability in 79 children with treatment-resistant non-self-limited focal epilepsies who had previously failed multiple ASMs. After a mean follow-up of 30 months, 54.4% of patients achieved a $\geq 50\%$ reduction in seizure frequency, including 5.1% who became seizure-free. Importantly, treatment response was maintained during long-term follow-up, with no significant differences in effectiveness observed at 12, 18, 24, and 30 months. These findings are particularly relevant given the highly treatment-resistant nature of our cohort and the limited evidence currently available regarding the long-term use of purified CBD in children with non-SELFEs.

Seizure improvement in our cohort was accompanied by favorable changes in interictal EEG abnormalities. Patients achieving a $\geq 50\%$ reduction in seizure frequency also showed improvement in focal

epileptiform abnormalities and bilateral discharges during wakefulness and sleep. These findings are consistent with previous studies suggesting that the effects of CBD may extend beyond clinical seizure reduction. In a prospective open-label study of children with treatment-resistant epilepsy, CBD treatment was associated with a significant reduction in the frequency of interictal epileptiform discharges, which correlated with the degree of seizure reduction [16]. Similarly, electrographic improvement has been reported in a retrospective cohort of patients with pediatric-onset refractory epilepsy treated with purified CBD, although a consistent association between specific EEG changes and clinical outcomes could not be established [17]. These findings suggest that the clinical response to CBD may be accompanied by improvement in interictal epileptiform activity, although the clinical significance of these EEG changes requires further investigation. Caregivers and treating physicians also reported cognitive and/or behavioral improvements in a proportion of patients; however, these observations should be interpreted cautiously because neuropsychological assessments were available in only 14 patients and were not systematically or uniformly performed.

CBD was generally well tolerated during long-term treatment. Adverse events were predominantly mild to moderate, transient, and manageable through adjustment of the CBD and/or concomitant ASM dose, and no serious treatment-related adverse events were observed. Drowsiness was the most frequently reported adverse event, occurring in 10 patients, five of whom were receiving concomitant clobazam. This finding is consistent with the well-described pharmacokinetic

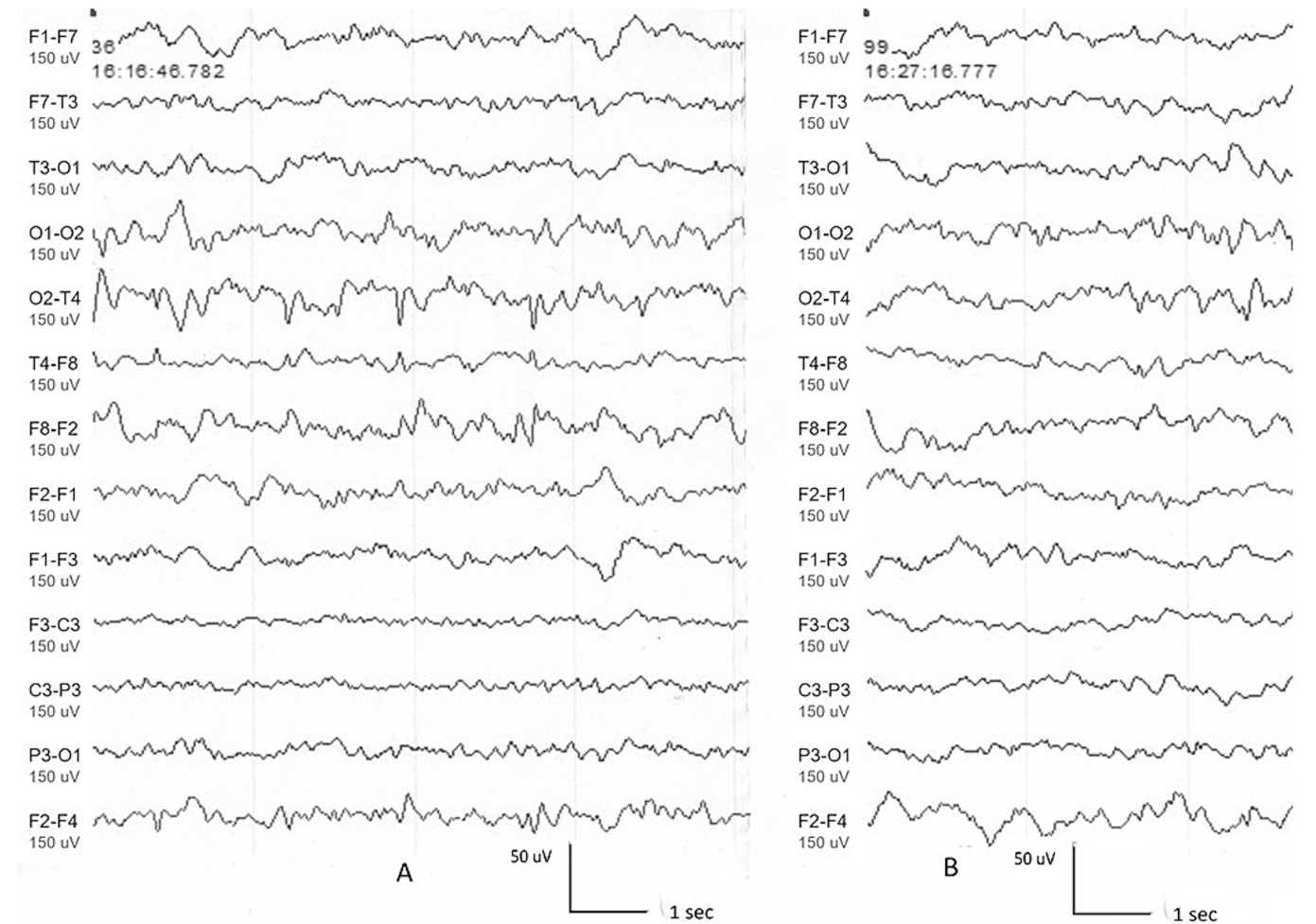


Fig. 2. EEG recordings from a 6-year-old girl with treatment-resistant focal epilepsy associated with tuberous sclerosis complex. (A) Sleep EEG before CBD initiation showing focal spikes over the right temporal region. (B) Sleep EEG obtained 1 month after CBD initiation, when the patient had become seizure-free, showing normalization of the EEG.

Table 1
Adverse events in 79 children with non-self-limited focal epilepsies treated with purified cannabidiol.

Adverse effects*	Number of patients 23 (29.1%)
Drowsiness	10 (12.7%)
Decreased appetite	5 (6.3%)
Behavioral disturbances	5 (6.3%)
Gastrointestinal symptoms	4 (5.1%)
Other**	2 (2.5%)

* Some patients experienced more than one adverse event; therefore, the sum of individual adverse events exceeds the number of patients with adverse events.

**Other effects included insomnia, dry mouth, blurred vision, and fever.

interaction between CBD and clobazam, whereby CBD inhibits CYP2C19-mediated metabolism of the active clobazam metabolite N-desmethyclobazam, increasing its exposure and potentially contributing to somnolence. In our patients, drowsiness improved after reduction of the clobazam and/or CBD dose [18]. Overall, the favorable tolerability observed in our cohort is consistent with the safety profile of purified CBD reported in randomized controlled trials and previous real-world studies [4,5,7,9,12,15].

In an open-label expanded-access study, Patel et al. [10] explored whether the effectiveness of CBD observed in patients with TSC might extend to focal epilepsies of other etiologies. Reductions in both focal and total seizure frequency were similar between patients with TSC and

those with non-TSC focal epilepsies. Our findings are consistent with these observations. In our multicenter real-world cohort, reductions in seizure frequency were observed in both TSC and non-TSC focal epilepsies, with no significant difference in responder rates between the two groups. However, given the relatively small TSC subgroup, these findings should be interpreted with some caution and confirmed in larger cohorts. These findings support further investigation of its use across a broader spectrum of treatment-resistant focal epilepsies.

CBD dosing in our study was individualized according to clinical response and tolerability, with doses of up to 40 mg/kg/day used in selected patients. When the initial response was absent or suboptimal, the dose was progressively increased when tolerated. Observational data from Szaflarski et al. [19] and Kühne et al. [12] have similarly suggested greater seizure reduction with higher CBD doses, and doses of up to 50 mg/kg/day have been used in Expanded Access Programs according to response and tolerability. However, any potential benefit of higher doses must be balanced against an increased risk of adverse events. In TSC, the recommended maintenance dose is 25 mg/kg/day, and when comparing doses of 25 and 50 mg/kg/day, no meaningful difference in efficacy was found, whereas adverse events were more frequent with the higher dose [10,15]. These observations support an individualized dosing strategy, with careful titration according to seizure response and tolerability.

Variability in CBD exposure should also be considered when interpreting treatment response. Plasma CBD concentrations were not measured in the present study, and treatment adherence and

Table 2

Demographic and electroclinical characteristics, treatment, and outcomes of 79 children with drug-resistant non-self-limited focal epilepsies treated with purified cannabidiol.

Characteristic	n (%) or median (range)
Patients	79
Sex	50 (63.3%)
Male	29 (36.7%)
Female	
Age, years	8 (2–13)
At epilepsy onset	9 (4–12)
At CBD initiation	
Family history of epilepsy	7 (8.9%)
First-degree relative	
Etiology	49 (62.0%)
Structural	30 (38.0%)
Unknown	
Seizure types*	28 (35.4%)
FMS with impaired consciousness	26 (32.9%)
FMS without impaired consciousness	22 (27.8%)
FNMS with impaired consciousness	21 (26.6%)
FNMS without impaired consciousness	
EEG abnormalities	36 (45.6%)
Focal	20 (25.3%)
Multifocal	23 (29.1%)
Focal and generalized	
CBD dose, mg/kg/day	34 (10–40)
Effectiveness	4 (5.1%)
Seizure-free	39 (49.4%)
50–99% reduction	36 (45.6%)
<50% reduction	0.0
Seizure increase	

* Patients could have more than one seizure type.

Abbreviations: CBD, cannabidiol; EEG, electroencephalography; FMS, focal motor seizures; FNMS, focal non-motor seizures.

administration in relation to meals were not systematically assessed. This is relevant because food intake can substantially influence CBD bioavailability. In our previous pharmacokinetic study in children with drug-resistant developmental and epileptic encephalopathies, administration of CBD with food increased maximum plasma concentration (C_{max}) by 41% and systemic exposure (AUC_{0–12}) by 45% compared with fasting conditions [20]. Although patients in the present study were advised to take CBD with a meal, adherence to this recommendation could not be systematically verified.

Another relevant finding was the persistence of treatment response over time. No significant reduction in effectiveness was observed at 12, 18, 24, or 30 months of follow-up, suggesting the absence of an apparent honeymoon effect in our cohort. This finding is consistent with the long-term open-label extension study by Thiele et al. [15], in which seizure reduction and responder rates were sustained throughout follow-up. In contrast, Kühne et al. [12], in a multicenter real-world study, observed a loss of effectiveness over time in approximately one-fifth of patients who had initially responded to CBD, suggesting a potential honeymoon effect. These differences may be related to differences in patient populations, epilepsy types, CBD doses, and follow-up duration. Further long-term studies are needed to determine whether some patients lose their response to CBD over time.

The potential contribution of placebo and expectation-related effects should also be considered when interpreting our findings. Placebo responses have been observed in randomized controlled trials of CBD in treatment-resistant pediatric epilepsies, with clinically relevant reductions in seizure frequency also occurring in placebo-treated patients [4,21]. In an open-label study such as ours, expectations of treatment benefit may additionally influence caregiver-reported outcomes. Because seizure frequency was primarily assessed using caregiver-completed seizure diaries, we cannot determine to what extent nonspecific treatment effects contributed to the observed response. Nevertheless, the sustained response during long-term follow-up and the improvement in interictal epileptiform abnormalities among responders

provide additional context to the reported clinical improvement.

It should also be considered that, irrespective of seizure type or etiology, some children with focal epilepsies may be at risk of evolving to developmental and/or epileptic encephalopathy with spike-wave activation in sleep (DEE-SWAS). Several clinical, neuroimaging, and EEG features have been associated with an increased risk of this evolution, including structural brain abnormalities such as polymicrogyria, hydrocephalus, and perinatal basal ganglia lesions; increasing seizure frequency or the emergence of additional seizure types, such as absence or myoclonic seizures; and increasing interictal epileptiform activity that becomes bilateral, often with frontal predominance, and is markedly activated during sleep. Recognition of these features is clinically relevant because early therapeutic intervention may potentially limit the impact of increasing sleep-activated epileptiform activity on neurodevelopment. In this context, CBD may represent a therapeutic option, particularly in patients showing an evolution toward the DEE-SWAS spectrum. In our previous study, 19 of 25 patients (76.0%) with DEE-SWAS achieved a favorable response to CBD treatment [22].

This study has several limitations. Its retrospective, multicenter design may have resulted in variability in data collection, clinical assessments, CBD dosing and titration, and follow-up practices across participating centers. The absence of a control group precludes establishing a causal relationship between CBD treatment and the observed outcomes. In addition, CBD dosing was individualized, and changes in concomitant ASMs or non-pharmacological therapies were required in a minority of patients during follow-up, potentially confounding the assessment of CBD effectiveness. Nevertheless, treatment modifications were kept to a minimum whenever clinically feasible, reflecting the challenges of maintaining an unchanged therapeutic regimen during long-term real-world management of children with treatment-resistant epilepsy. The sample size also limited the statistical power of subgroup analyses, particularly the comparison between patients with TSC (n=13) and those with non-TSC focal epilepsies. Therefore, the absence of a significant difference between these groups should be interpreted with caution. In addition, the relatively small number of patients recruited at individual centers limited the assessment of potential center effects. EEG assessments were not centrally reviewed, and neuropsychological evaluations were neither systematic nor standardized; therefore, the observed EEG and cognitive or behavioral improvements should be considered exploratory. These findings should be confirmed in prospective studies using standardized outcome assessments and, ideally, randomized controlled designs. Finally, all patients received the same pharmaceutical-grade purified CBD formulation approved in Argentina, which may limit the generalizability of our findings to other CBD products.

Despite these limitations, our study has several strengths. It provides multicenter real-world data specifically addressing purified CBD in a relatively well-characterized cohort of children with treatment-resistant non-SeLFEs, a population for which evidence remains scarce. The relatively long follow-up allowed assessment not only of initial seizure response but also of the durability of treatment effectiveness and tolerability. Furthermore, the inclusion of patients with different focal epilepsy etiologies and seizure types reflects the heterogeneity encountered in routine clinical practice. Taken together, these findings complement evidence from controlled trials and broaden the available real-world experience with purified CBD.

5. Conclusion

Adjunctive purified CBD was associated with sustained seizure reduction and good long-term tolerability in children with treatment-resistant non-self-limited focal epilepsies, with more than half achieving a ≥50% reduction in seizure frequency. Treatment was administered using variable, individualized doses according to clinical response and tolerability, supporting a patient-tailored approach to CBD therapy. Responses were observed in both TSC and non-TSC focal

epilepsies, suggesting that the potential therapeutic benefits of CBD warrant further investigation across different etiologies of focal epilepsy.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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

CRedit authorship contribution statement

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

References

- [1] Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, et al. International league against epilepsy classification and definition of epilepsy syndromes with onset in childhood: position paper by the ILAE task force on nosology and definitions. *Epilepsia* 2022;63(6):1398–442. <https://doi.org/10.1111/epi.17241>.
- [2] Cross JH, Reilly C, Gutierrez Delicado E, Smith ML, Malmgren K. Epilepsy surgery for children and adolescents: evidence-based but underused. *Lancet Child Adolesc Health* 2022;6(7):484–94. [https://doi.org/10.1016/S2352-4642\(22\)00098-0](https://doi.org/10.1016/S2352-4642(22)00098-0). Epub 2022 May 12 PMID: 35568054.
- [3] Matricardi S, Scorrano G, Prezioso G, Burchiani B, Di Cara G, Striano P, et al. The latest advances in the pharmacological management of focal epilepsies in children: a narrative review. *Expert Rev Neurother* 2024;24(4):371–81. <https://doi.org/10.1080/14737175.2024.2326606>.
- [4] Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med* 2017;376(21):2011–20. <https://doi.org/10.1056/NEJMoa1611618>.
- [5] Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. GWPCARE3 study group. Effect of cannabidiol on drop seizures in the lennox-gastaut syndrome. *N Engl J Med* 2018;378(20):1888–97. <https://doi.org/10.1056/NEJMoa1714631>.
- [6] Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. GWPCARE4 study group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018;391(10125):1085–96. [https://doi.org/10.1016/S0140-6736\(18\)30136-3](https://doi.org/10.1016/S0140-6736(18)30136-3).
- [7] Thiele EA, Bebin EM, Bhatthal H, Jansen FE, Kotulska K, Lawson JA, et al. GWPCARE6 study group. Add-on cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex: a placebo-controlled randomized clinical trial. *JAMA Neurol* 2021;78(3):285–92. <https://doi.org/10.1001/jamaneurol.2020.4607>.
- [8] Devinsky O, Verducci C, Thiele EA, Laux LC, Patel AD, Filloux F, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. *Epilepsy Behav* 2018;86:131–7. <https://doi.org/10.1016/j.yebeh.2018.05.013>.
- [9] Cerulli Irelli E, Mazzeo A, Caraballo RH, Perulli M, Moloney PB, Peña-Ceballos J, et al.; GENE-CBD study group; Orsini A, Coppola A. Expanding the therapeutic role of highly purified cannabidiol in monogenic epilepsies: a multicenter real-world study. *Epilepsia*. 2025;66(7):2253–67. doi: 10.1111/epi.18378.
- [10] Patel AD, Szaflarski JP, Lyons PD, Boffa M, Greco T, Saurer TB, et al. Long-term efficacy and safety of cannabidiol in patients with treatment-resistant focal epilepsies treated in the expanded access program. *Epilepsia* 2025;66(10):3730–40. <https://doi.org/10.1111/epi.18496>.
- [11] Kochen S, Villanueva M, Bayarres L, Daza-Restrepo A, Gonzalez Martinez S, Oddo S. Cannabidiol as an adjuvant treatment in adults with drug-resistant focal epilepsy. *Epilepsy Behav* 2023;144:109210. <https://doi.org/10.1016/j.yebeh.2023.109210>.
- [12] Kühne F, Becker LL, Bast T, Bertsche A, Borggraefe I, Boßelmann CM, et al. Real-world data on cannabidiol treatment of various epilepsy subtypes: a retrospective, multicenter study. *Epilepsia Open* 2023;8(2):360–70. <https://doi.org/10.1002/epi4.12699>.
- [13] Hollander M, Mayer T, Klotz KA, Knake S, von Podewils F, Kurlmann G, et al. Use of cannabidiol for off-label treatment of patients with refractory focal, genetic generalised and other epilepsies. *Neurol Res Pract* 2025;7(1):49. <https://doi.org/10.1186/s42466-025-00408-w>.
- [14] Beniczky S, Trinka E, Wirrell E, Abdulla F, Al Baradie R, Alonso Vanegas M, et al. Updated classification of epileptic seizures: position paper of the international league against epilepsy. *Epilepsia* 2025;66(6):1804–23. <https://doi.org/10.1111/epi.18338>.
- [15] Thiele EA, Bebin EM, Filloux F, Kwan P, Loftus R, Sahebkar F, et al. Long-term cannabidiol treatment for seizures in patients with tuberous sclerosis complex: an open-label extension trial. *Epilepsia* 2022;63(2):426–39. <https://doi.org/10.1111/epi.17150>.
- [16] Klotz KA, Grob D, Schönberger J, Nakamura L, Metternich B, Schulze-Bonhage A, et al. Effect of cannabidiol on interictal epileptiform activity and sleep architecture in children with intractable epilepsy: a prospective open-label study. *CNS Drugs* 2021;35(11):1207–15. <https://doi.org/10.1007/s40263-021-00867-0>.
- [17] Herlopian A, Barnett JR, Nascimento FA, Lee H, Thiele EA. Electroencephalographic changes in purified pharmaceutical cannabidiol therapy. *Epilepsy Behav* 2022;128:108558. <https://doi.org/10.1016/j.yebeh.2022.108558>. Epub 2022 Jan 22 PMID: 35078115.
- [18] Morrison G, Crockett J, Blakey G, Sommerville K. A phase 1, open-label, pharmacokinetic trial to investigate possible drug-drug interactions between clobazam, stiripentol, or valproate and cannabidiol in healthy subjects. *Clin Pharmacol Drug Dev* 2019;8(8):1009–31. <https://doi.org/10.1002/cpdd.665>.
- [19] Szaflarski JP, Hernandez K, Bebin EM, Gaston TE, Grayson LE, Ampah SB, et al. Higher cannabidiol plasma levels are associated with better seizure response following treatment with a pharmaceutical grade cannabidiol. *Epilepsy Behav* 2019;95:131–6.
- [20] Brstilo L, Valenzuela GR, Ibarra M, Guido PC, Bressan I, Marin N, et al. Population pharmacokinetics of cannabidiol and the impact of food and formulation on systemic exposure in children with drug-resistant developmental and epileptic encephalopathies. *Epilepsia* 2025;66(4):1143–54. <https://doi.org/10.1111/epi.18255>.
- [21] Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, et al.; GWPCARE2 study group. Dose-ranging effect of adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in dravet syndrome: a randomized clinical trial. *JAMA Neurol* 2020;77(5):613–621. doi: 10.1001/jamaneurol.2020.0073. Erratum in: *JAMA Neurol*. 2020 May 1;77(5):655. doi: 10.1001/jamaneurol.2020.0749.
- [22] Reyes Valenzuela G, Espeche A, Fortini S, Gamboni B, Adi J, Semprino M, et al. A multicenter study on the use of purified cannabidiol for children with treatment-resistant developmental and epileptic encephalopathies. *Epilepsy Behav* 2025;171:110590. <https://doi.org/10.1016/j.yebeh.2025.110590>.