Received: 12 March 2025 | Revised: 6 May 2025 | Accepted: 12 May 2025

DOI: 10.1002/epi4.70078

Epilepsia Open® Open Access

ORIGINAL ARTICLE

Is highly purified cannabidiol a treatment opportunity for drug-resistant epilepsy in subjects with typical Rett syndrome and CDKL5 deficiency disorder?

Aglaia Vignoli[1,2] | **Giulia Prato**[3] | **Enrico Alfei**[4] | **Irene Bagnasco**[5] | **Alberto Danieli**[6] | **Massimiliano Celario**[7,8] | **Jacopo Favaro**[9,10] | **Sara Matricardi**[11] | **Francesca Felicia Operto**[12] | **Alessandro Orsini**[13] | **Davide Paolo Bernasconi**[14,15] | **Nicola Pietrafusa**[16] | **Emilia Ricci**[2,17] | **Luca Manfredini**[18] | **Giulia Balletto**[3] | **Paolo Bonanni**[6] | **Maria Paola Canevini**[2,17] | **Valentina De Giorgis**[7,8] | **Lino Nobili**[3] | **Stefano Sartori**[9,10] | **Miriam Nella Savini**[17] | **Ilaria Viganò**[17] | **Nicola Specchio**[16,19]

Correspondence
Aglaia Vignoli, Childhood and Adolescence Neuropsychiatry Unit, Grande Ospedale Metropolitano Niguarda, Milan, Italy.
Email: aglaia.vignoli@unimi.it

Funding information
Italian Ministry of Health, Grant/Award Number: MCNT2-2023-12377646; Ministry of University and Research (MUR); National Recovery and Resilience Plan (NRRP), Grant/Award Number: MNESYS (PE0000006)

Abstract

Objective: This study aimed to evaluate the efficacy and safety of adjunctive, highly purified Cannabidiol (Epidiolex®) in individuals with drug-resistant epilepsy (DRE) due to genetically determined typical Rett Syndrome (RTT) and CDKL5 Deficiency Disorder (CDD).

Methods: We recruited subjects with genetically confirmed typical RTT and CDD with drug-resistant seizures who received add-on treatment with highly purified Cannabidiol (CBD) through a national collaboration group. CBD treatment was titrated from 5 to 20 mg/kg/day; concurrent antiseizure medications (ASMs) could have been adjusted as clinically indicated.

Results: We enrolled 27 subjects (26 females), carrying a *MECP2* genetic variant (14 subjects, 51.9%) or a *CDKL5* genetic variant (13 subjects, 48.1%). Median age [IRQ] of individuals was 10.5 [7.9, 18.5] years. The median dose of CBD [IRQ] at last follow-up was 15 [11.12, 18.8] mg/kg/day, in association with a mean of 3 ASMs (range 2–4). The median duration of treatment was 14 [8.5, 20] months. Although not reaching a significant statistical effect, CBD reduced the incidence of seizures with respect to the baseline in 18/27 (66.6%) subjects, with 7 (25.9%) showing a seizure reduction >75%, and 11 (40.7%) >50%. The most relevant adverse events were somnolence seen in 3 subjects, irritability/agitation in 2 subjects, loss of appetite in 2 subjects, and insomnia in 1 individual. Caregivers

For affiliations refer to page 1117.

reported an improvement in attention and reactivity in 12 subjects (44.4%), in sleep quality in 5 subjects (18.5%), and in motor aspects in 3 patients (11.1%).

Significance: CBD resulted effective in reducing seizure frequency in 66.6% of the study sample, regardless of the pathogenic variant; side effects were mild, and caregivers reported an improvement in behavioral and motor features.

Plain Language Summary: This study explored the use of highly purified Cannabidiol (CBD, Epidiolex®) as an add-on therapy for individuals with drug-resistant epilepsy due to Rett Syndrome (RTT) or CDKL5 Deficiency Disorder (CDD). Twenty-seven participants received CBD alongside their usual ASMs. After a median treatment duration of 14 months, 66.6% experienced fewer seizures, with some showing over 75% reduction. Side effects were generally mild, mainly sleepiness or irritability. Notably, caregivers reported improvements in attention, responsiveness, sleep, and motor function. While results were not statistically significant, they suggest CBD may benefit seizure control and quality of life in RTT and CDD patients.

KEYWORDS

cannabidiol, CDKL5 deficiency disorder, drug-resistant epilepsy, Rett syndrome

1 | INTRODUCTION

Rett syndrome (RTT) is an X-linked-dominant neurodevelopmental disorder caused by pathogenic variants in the *MECP2* gene, characterized by cognitive and communicative regression, loss of hand use, and midline hand stereotypies. Diagnosis in these patients is primarily clinical, based on specific criteria updated by the Rett Search Consortium in 2010,[1] which distinguish between typical and atypical forms of RTT.

Although epilepsy is not part of the formal diagnostic criteria,[1] it is a core symptom, experienced by 68.1% of patients, with 32.6% presenting uncontrolled seizures.[2]

In CDKL5 Deficiency Disorder (CDD), early-onset refractory seizures are a constant feature, along with global developmental delays, hand stereotypies, severe hypotonia, sleep disturbances, and gastrointestinal issues.[3] Initially thought to be an atypical variant of RTT, due to the similar core features of RTT, CDD is now recognized as a distinct developmental and epileptic encephalopathy (DEE) caused by genetic variants in the *CDKL5* gene, also X-linked.[4] The intractable nature of seizures in CDD has led caregivers and clinicians to explore alternative treatments such as the ketogenic diet and vagal nerve stimulation, in addition to conventional anti-seizure medications (ASMs).[5,6] In a caregiver survey, over two-thirds reported that artisanal cannabis products improved seizure control, and additional benefits included enhanced alertness, attention, cognition, sleep, mood, development, and appetite.[7]

Key points

- This study explored whether highly purified Cannabidiol (Epidiolex®) could help manage drug-resistant seizures in people with RTT or CDD.
- Twenty-seven genetically confirmed patients (median age 10.5 years) received CBD titrated up to 20 mg/kg/day alongside their usual antiseizure medications.
- After a median of 14 months, 66.6% showed a reduction in seizures; 25.9% had over 75% reduction.
- Reported side effects were generally mild, including somnolence, irritability, and appetite loss.
- Many caregivers observed positive changes beyond seizure control, including better attention, improved sleep, and enhanced motor function.

Recently, highly purified cannabidiol (Epidiolex®) has been approved for the treatment of a few DEEs, such as Lennox–Gastaut (LGS), Dravet syndromes (DS), and Tuberous Sclerosis Complex (TSC), and has shown efficacy in placebo-controlled and open-label trials.[8–11] In

open-label trials among patients with childhood-onset drug-resistant epilepsy (DRE), cannabinoids have also been tested in subjects with atypical RTT, showing *CDKL5* or *FOXG1* pathogenic variants.[10,11]

The available data on cannabinoids used for the RTT subject's concerns cannabidivarin (CBDV), the propyl analog of CBD.[12] In this preclinical phase I study, the treatment of five patients with RTT with CBDV showed improved seizure control. Four patients reduced their baseline ASMs after CBDV initiation, and hypersomnolence and drooling were the only identified drug-related adverse events.

In a recent study, the efficacy and tolerability of Epidiolex® on seizure control was evaluated in a sample of 10 out of 26 subjects with epilepsy in RTT as well as its effects on psychiatric symptoms and motor functions. CBD reduced the incidence of seizures in 70% of subjects, reduced agitation and/or anxiety attacks in 50%, and improved spasticity in 40%. No adverse events were observed, even though 50% of subjects had clobazam in association. Indeed, only one subject experienced a transitory drooling and somnolence episode at the CBD initiation.[13]

Since some patients with RTT or CDD may show features similar to LGS, we carried out a multicenter study on patients treated with CBD for at least 6 months, reporting on its effectiveness and safety in a large group with drug-resistant epilepsy caused by genetically confirmed typical RTT or CDD.

2 | METHODS

We recruited through a national collaboration group (CBD-RTT Syndrome Study Group) subjects with genetically confirmed typical RTT and CDD with drug-resistant seizures who were receiving add-on treatment with highly purified CBD (Epidiolex®). Patients were included if, as of January 2024, they (1) were postregression (≥6 months after the last loss of hand use, speech, or gross motor regression), (2) had been receiving add-on treatment with highly purified CBD due to inadequate seizure control for at least 6 months, and (3) had maintained a stable dosage of ASMs for more than 4 weeks prior to CBD initiation.

CBD treatment was titrated from 5 to 20 mg/kg/day, depending on tolerability and efficacy; both the CBD dosage and concurrent ASM regimens could be adjusted as clinically indicated. We collected demographic, clinical, and genetic data through the referring physician, including age, gender, genetic variants (*MECP2*/*CDKL5*), age at seizure onset, seizure types, CBD dosage at the last follow-up, and concurrent ASMs.

Seizure types were classified according to the ILAE classification,[14] and seizure frequency was reported as daily, weekly, or monthly. A positive response to treatment was defined as a reduction >50% in seizure frequency compared to baseline levels (4 weeks before CBD initiation).

Safety was assessed by recording adverse events through caregivers' interviews and clinical examinations of the patient. Caregivers were also interviewed to gather additional information on sleep characteristics, behavioral changes, and overall quality of life, though only a small proportion of patients had completed specific questionnaires (The Sleep Disturbance Scale for Children—SDSC, the Quality of Life Inventory-Disability—QI-Disability and Parental Stress Index—PSI).

Parents provided consent for the use of anonymized personal data for scientific purposes, in accordance with the ethical standards of the 1964 Declaration of Helsinki. The Ethics Committee of San Paolo Hospital, Milan approved the study (2019/ST/098).

2.1 | Statistical methods

We calculated the proportion of patients who had ≥50% reduced seizure frequency with the 95% confidence interval (Clopper-Pearson method). To compare the proportion of responders between the RTT and CDD subgroups, we used Fisher's exact test. The association between age and seizure reduction was analyzed using the Kruskal–Wallis test, while the relationship between behavioral improvement and seizure reduction was examined using the Fisher's exact test.

3 | RESULTS

3.1 | Clinical characteristics (Table 1)

We enrolled 27 subjects (26 females), with a genetically proven typical RTT carrying a *MECP2* genetic variant (14 subjects, 51.9%) or CDD carrying a *CDKL5* genetic variant (13 subjects, 48.1%).

Median age [IRQ] of individuals was 10.5 [7.9, 18.5] years. Most of the subjects experienced different seizure types. Tonic seizures (10 subjects, 37.0%), generalized tonic–clonic seizures (7 subjects, 25.9%) or focal seizures (5 subjects, 18.5%) were the most representative ones. Other seizure types reported were epileptic spasms (3 subjects, 11.1%) and atypical absences (1 subject, 3.7%).

3.2 | CBD treatment: Efficacy and safety

The median dose of CBD [IRQ] at last follow-up was 15 [11.12, 18.8] mg/kg/day. The median duration of treatment was 14 [8.5, 20] months.

TABLE 1 Clinical characteristics.

Variables	Levels	Overall sample $N=27$
Sex (%)	F	26 (96.3)
	M	1 (3.7)
Age, years (median [IQR])		10.5 [7.9, 18.5]
Pathogenic variant	*MECP2*	14 (51.9)
	CDKL5	13 (48.1)
CBD dosage at last follow-up (mg/kg) (median [IQR])		15 [11.12, 18.8]
Seizure semeiology (%)	Atypical absences	1 (3.7)
	Focal seizures	5 (18.5)
	Myoclonic seizures	1 (3.7)
	Tonic seizures	10 (37.0)
	Bilateral tonic–clonic seizures	7 (25.9)
	Spasms	3 (11.1)
Follow-up, months (median [IQR])		14 [8, 20]
Outcome at last follow-up (seizure reduction) (%)	>50%	11 (40.7)
	>75%	7 (25.9)
	No change	9 (33.3)
Behavioral effects (%)	Improvement	14 (51.9)
	No change	13 (48.1)

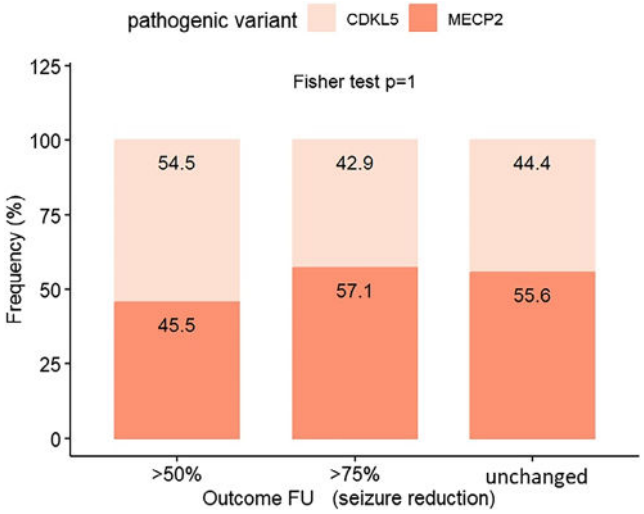

FIGURE 1 Relationship between pathogenic variant and seizure outcome.

CBD was associated with a mean of 3 ASMs (range 2–4), including clobazam (CLB; 18/27), carbamazepine (CBZ; 10/27), valproic acid (VPA; 9/27), levetiracetam (LEV; 5/27), lamotrigine (LTG; 5/27), vigabatrin (GVG; 4/27), rufinamide (RUF; 2/27), phenobarbital (PB; 3/27), zonisamide (ZNM; 2/27), felbamate (FLB; 1/27), lacosamide (LCS; 2/27), clonazepam (CZP; 2/27), and topiramate (TPM; 3/27).

CBD reduced seizure frequency by ≥50% in 18 (66.6%, 95% CI: 46.0%–83.5%) subjects, with 7 (25.9%) experiencing a reduction >75%. The lower limit of the confidence interval indicates that the true proportion of patients with seizure frequency ≥50% is not lower than 46%. No seizure aggravation was observed. Among the genetic subgroups, a seizure reduction of ≥50% was observed in 9/14 RTT subjects (64.3%) and 9/13 CDD subjects (69.2%). The Fisher's exact test ($p=1.0$) showed no statistically significant difference between the two groups, suggesting that CBD had comparable effectiveness in both RTT and CDD (Figure 1).

Regarding seizure types, we found that tonic seizures were particularly reduced in both groups of subjects, while epileptic spasms in the CDD group. There was no difference between RTT subjects who had a reduction in seizure frequency and those who did not regarding the age at diagnosis of RTT, the age at onset of epilepsy, and the number and type of associated ASMs.

CBD was well tolerated by the great majority of the subjects: the most relevant adverse events were somnolence reported in 3 subjects, irritability/agitation in 2 subjects, loss of appetite in 2 subjects, and insomnia in one subject. An adverse event was responsible for drug withdrawal in 2 subjects (one for irritability/agitation, one for loss of appetite).

3.3 | CBD treatment: Behavioral and motor outcomes

Although we did not conduct a standardized evaluation in our RTT/CDD cohort, we systematically gathered parents' assessments of their children's behavior during CBD treatment. Improvements were reported in attention and reactivity in 12 subjects (44.4%), sleep quality in 5 subjects (18.5%)—with reductions in sleep onset time and nocturnal awakenings—and motor function in 3 subjects (11.1%). Specifically, tremor decreased in one subject, ambulation became more stable in another, and one individual showed improvement in hyperkinetic movement disorder. We considered whether the improvement in behavior with a significant reduction in agitation could be related to an improvement in seizure control, and we report a trend toward a greater behavioral impact in those with a major seizure reduction (Figure 2).

The analysis of the association between age, genetics, and behavioral effects with seizure outcome is reported in Table 2.

4 | DISCUSSION

Our findings suggest a strong trend toward the efficacy of CBD in reducing seizure frequency, with 66.6% of subjects experiencing a ≥50% reduction and 25.9% achieving a >75% reduction. The consistency of the response, combined with the absence of seizure aggravation and a favorable safety profile, highlights purified cannabidiol (Epidiolex®) CBD as a promising therapeutic option for individuals with RTT and CDD. Moreover, beyond seizure control, a substantial proportion of patients also showed improvements in behavior, attention, and reactivity—especially among those who responded to treatment—further supporting the potential benefits of CBD in this population.

Cannabidiol has attracted considerable attention for its potential therapeutic benefits across various epileptic syndromes, including neurodevelopmental disorders like Rett Syndrome and CDD. Recent systematic reviews have demonstrated the effectiveness of CBD in individuals with various genetic disorders that are common causes of epileptic encephalopathies, including studies supporting its use in CDD and MECP2-related disorders.[15] While research is ongoing, some studies suggest that CBD may have positive effects in these conditions, useful both for seizure control and behavioral aspects.[7,12,13] However, further research is needed to definitively establish its safety and efficacy.

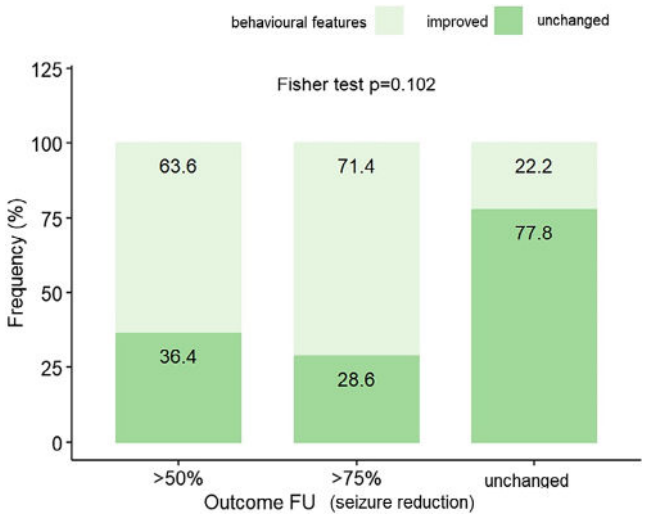

FIGURE 2 Relationship between seizure outcome and behavioral changes.

The prevalence of active seizures in individuals with typical RTT ranges from 30% to 44%,[2,16] with no specific association between *MECP2* pathogenic variants and either seizure prevalence or severity. Although epilepsy in RTT can persist throughout life,[16,17] only limited studies have identified the most suitable ASM regimen for different age groups.[2,18–20]

Notably, a diagnosis of atypical RTT with a severe clinical phenotype has been linked to a higher prevalence of epilepsy compared to classic RTT.[3] In cases of CDD, achieving complete seizure freedom is exceedingly rare.

A recently published international study investigating caregiver perspectives on ASMs used by 399 children and adults with CDD reported that the most common ASMs used were LEV, TPM, VPA, GVG, PB, and CLB depending on the age of the patient. Data about cannabidiol use was difficult to evaluate, as there was significant variation in the types of cannabis derivatives, and only a few subjects were treated with Epidiolex®.[21]

Given the high refractoriness of seizures in CDD, there is a particular need for new ASMs and alternative treatment options. Encouraging results of the efficacy of ganaxolone in CDD emerged from the double-blind, randomized, placebo-controlled study specifically for motor seizures, where there was a median percentage change in 28-day seizure frequency of −30.7% (IQR −49.5 to −1.9) in the ganaxolone group with respect to placebo.[22] The open-label extension follow-up[23] confirmed the results, with a median of seizure reduction of 48.2% and a good safety profile.

A potential role for fenfluramine is developing for different DEEs, including CDD.[24] Currently, an international multicentric Phase 3 study is ongoing (ClinicalTrails.gov NCT03861871), while there is no evidence of its potential use in typical RTT.

TABLE 2 Analysis of the association between age, genetics, and behavioral effects with seizure outcome.

Variables	Levels	No change $N=9$	>50% $N=11$	>75% $N=7$	*p*-Value
Pathogenic variant (%)	*MECP2*	5 (55.6)	5 (45.5)	4 (57.1)	1[a]
	CDKL5	4 (44.4)	6 (54.5)	3 (42.9)	
Age, years (median [IQR])		8 [6.5, 14]	9.3 [8.4, 21]	11 [10.25, 21]	0.329[b]
Behavioral effects (%)	Improvement	2 (22.2)	7 (63.6)	5 (71.4)	0.102[a]
	No change	7 (77.8)	4 (36.4)	2 (28.6)	

[a]Fisher test.
[b]Kruskal–Wallis test.

Aside from considering the efficacy of ASMs in individuals with both typical RTT and CDD, another relevant factor is tolerability. The clinical condition of these individuals is often complicated by multiple neurological issues (e.g., hypotonia, stereotypies, sleep disorders), gastrointestinal disturbances, bone health concerns, and communication challenges, making therapeutic choices particularly difficult. Indeed, due to the numerous comorbidities, these individuals are often forced to take multiple therapies. Therefore, a drug that acts on both seizures and behavioral aspects, with minimal interactions, would be highly advantageous.

In this context, assessing the potential impact of new treatments for people with rare disorders associated with drug-resistant seizures is essential.

A recent paper[13] indicated that CBD is effective and well-tolerated in patients with typical RTT and DRE. Our experience aligns with these findings, with nearly 70% of individuals showing a favorable clinical response and experiencing a reduction in mean monthly seizure frequency of more than 50%. No cases of epilepsy worsening were observed. Previous studies on CBD treatment in CDD,[10] as well as caregiver reports,[7] have also demonstrated a positive efficacy profile.

The results of our study demonstrated that CBD is effective in reducing seizure frequency in 66.6% of the patients, regardless of the pathogenic variant, concomitant ASMs, and epilepsy duration.

We examined the types of seizures most responsive to CBD treatment and found that individuals with tonic seizures, in both typical RTT and CDD, experienced a greater reduction. This outcome aligns with observations in LGS and Dravet Syndrome.[25] Notably, epileptic spasms, which are generally resistant to conventional ASMs, have shown responsiveness to CBD treatment in CDD, as recently reported in drug-resistant infantile epileptic spasms syndrome.[26]

Regarding tolerability, our study demonstrated a favorable CBD tolerance profile. We typically employ a very slow titration in these patients due to their fragility and sensitivity to even minimal changes in medication. We also kept low dosages of CBD in order to preserve tolerability. Indeed, CBD was generally well tolerated, and no serious adverse events were reported.

Among the side effects, somnolence was the most common. All individuals who experienced daytime somnolence were also receiving concurrent treatment with CLB. Drug–drug interactions between CLB and CBD have been demonstrated in both animal models and human studies, and this interaction may contribute to somnolence due to an increase in CLB's active metabolite, N-desmethylclobazam (N-clobazam).[27] Effective management of concomitant ASMs is essential to minimize the occurrence of side effects.

In severe developmental encephalopathies like RTT, the prospect of addressing aspects of the disease beyond seizure control is challenging. Indeed, parents reported improvements in attention and social interaction among patients with typical RTT and CDD, even independent of seizure reduction, as highlighted also in other real-life experiences.[28,29] Another significant area of improvement was postural tone, stability, and movement disorders. This benefit has also been noted in patients with LGS and could potentially be explained by CBD's effect on brain locomotor centers.[30]

Additionally, the positive effect of CBD on sleep regulation, previously reported in other patient groups,[31,32] was confirmed in our cohort.

5 | LIMITATIONS

Our study has several limitations, including a relatively small sample size, which is understandable given the rarity of these disorders. The small number of subjects prevented us from conducting a meaningful comparative analysis, so statistical evaluations were kept descriptive. Furthermore, the study's lack of a control group and its retrospective design are additional limitations, which did not allow administering tests in a standardized manner. Nonetheless, our findings underpin the importance of exploring new therapeutic options for rare genetic syndromes with DRE in real-world clinical settings.

6 | CLINICAL RELEVANCE/ FUTURE DIRECTIONS

Findings from our study further contribute to the understanding of the available treatments for DRE in typical RTT and CDD, focusing on real-world experience of CBD use in these patients. However, for individuals with these rare genetic disorders, identifying the optimal treatment approaches for seizure control continues to be a high priority for further research, in order to reduce the seizure burden and to optimize the balance between side effects and seizure control. Finally, the preliminary findings derived from our limited cohort underscore the necessity for large-scale registries and prospective studies to substantiate these results and to potentially extend the therapeutic application of CBD, with a focus on seizure types or behavioral conditions most likely to benefit from such treatment.

AUTHOR CONTRIBUTIONS

Aglaia Vignoli conceived and designed the study, collected and analyzed data, and wrote the manuscript. Giulia Prato collected and analyzed data, wrote the manuscript. Irene

Bagnasco, Alberto Danieli, Massimiliano Celario, Jacopo Favaro, Francesca Felicia Operto, Alessandro Orsini, Nicola Pietrafusa, Emilia Ricci, Luca Manfredini, Giulia Balletto, Paolo Bonanni, Valentina De Giorgis, Miriam Nella Savini, and Ilaria Viganò—collected data. Davide Paolo Bernasconi performed statistical analysis. Maria Paola Canevini reviewed the manuscript. Lino Nobili interpreted data and reviewed the manuscript. Stefano Sartori contributed to the writing of the manuscript. Nicola Specchio conceived and designed the study; supervised all the study development and revised the manuscript.

AFFILIATIONS

[1]Childhood and Adolescence Neuropsychiatry Unit, Grande Ospedale Metropolitano Niguarda, Milan, Italy

[2]Health Sciences Department, Università degli Studi di Milano, Milan, Italy

[3]Unit of Child Neuropsychiatry, IRCCS Istituto Giannina Gaslini, Full Member of European Reference Network EpiCARE, Genoa, Italy

[4]Pediatric Neurology Unit, Buzzi Children's Hospital, Milan, Italy

[5]Division of Child Neuropsychiatry, Martini Hospital, Torino, Italy

[6]Epilepsy Unit, IRCCS E. Medea Scientific Institute, Conegliano, Italy

[7]Department of Child Neurology and Psychiatry, IRCCS Mondino Foundation, Pavia, Italy

[8]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

[9]Department of Women's and Child's Health, University of Padua, Padova, Italy

[10]Paediatric Neurology and Neurophysiology Unit – University Hospital of Padua, Padova, Italy

[11]Department of Pediatrics, University of Chieti, Chieti, Italy

[12]Department of Science of Health School of Medicine, University Magna Greacia of Catanzaro, Catanzaro, Italy

[13]Pediatric Neurology, University Hospital of Pisa, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy

[14]Bicocca Bioinformatics Biostatistics and Bioimaging Center, School of Medicine and Surgery, University of Milano-Bicocca, Italy

[15]Clinical Research and Innovation Unit, Grande Ospedale Metropolitano Niguarda, Milan, Italy

[16]Neurology, Epilepsy and Movement Disorders Unit, Bambino Gesù Children's Hospital IRCCS, Full Member of European Reference Network EpiCARE, Rome, Italy

[17]Child Neurology Unit, Epilepsy Center, San Paolo Hospital, Member of European Reference Network EpiCARE, Milan, Italy

[18]Paediatric Chronic Pain and Palliative Care Service, IRCCS Istituto Giannina Gaslini, Genoa, Italy

[19]University Hospitals KU Leuven, Leuven, Belgium

ACKNOWLEDGMENTS

The authors thank all patients and families for their essential support and EpiCARE *European Reference Network* for rare and complex epilepsies. Open access publishing facilitated by Universita degli Studi di Milano, as part of the Wiley - CRUI-CARE agreement.

FUNDING INFORMATION

AV received research funding from Fondazione Telethon (Project GSA23G001—Targeting the gut to improve seizure control in CDD) and the Italian Ministry of Health (PNRR—NextGenerationEU), project PNRR-MCNT2-2023-12377646—MiCrobiota-gut–brain Axis in Resistant Epilepsy (CARE). NS and NP were supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006)—A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022). NS and NP were also supported by the Italian Ministry of Health with Current Research Funds.

CONFLICT OF INTEREST STATEMENT

AV has served as a consultant for Anavex, Acadia, and GW Pharmaceuticals and has conducted clinical trials with Newron Pharmaceuticals. NS has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus and Takeda; has received speaker honoraria from Eisai, BioMarin, LivaNova, Sanofi; has served as an investigator for Zogenix, Marinus, BioMarin, UCB, Roche. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Aglaia Vignoli https://orcid.org/0000-0003-4638-4663
Jacopo Favaro https://orcid.org/0000-0002-4340-2398
Francesca Felicia Operto https://orcid.org/0000-0002-2444-8761
Valentina De Giorgis https://orcid.org/0000-0002-5828-7070
Lino Nobili https://orcid.org/0000-0001-9317-5405
Stefano Sartori https://orcid.org/0000-0002-0012-6848

REFERENCES

1. Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010;68(6):944–50. https://doi.org/10.1002/ana.22124

2. Nissenkorn A, Levy-Drummer RS, Bondi O, Renieri A, Villard L, Mari F, et al. Epilepsy in Rett syndrome--lessons from the Rett networked database. Epilepsia. 2015;56(4):569–76. https://doi.org/10.1111/epi.12941
3. Mangatt M, Wong K, Anderson B, Epstein A, Hodgetts S, Leonard H, et al. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome. Orphanet J Rare Dis. 2016;11:39. https://doi.org/10.1186/s13023-016-0418-y
4. Leonard H, Downs J, Benke TA, Swanson L, Olson H, Demarest S. CDKL5 deficiency disorder: clinical features, diagnosis, and management. Lancet Neurol. 2022;21(6):563–76. https://doi.org/10.1016/S1474-4422(22)00035-7
5. Lim Z, Wong K, Olson HE, Bergin AM, Downs J, Leonard H. Use of the ketogenic diet to manage refractory epilepsy in CDKL5 disorder: experience of >100 patients. Epilepsia. 2017;58(8):1415–22. https://doi.org/10.1111/epi.13813
6. Lim Z, Wong K, Downs J, Bebbington K, Demarest S, Leonard H. Vagus nerve stimulation for the treatment of refractory epilepsy in the CDKL5 deficiency disorder. Epilepsy Res. 2018;146:36–40. https://doi.org/10.1016/j.eplepsyres.2018.07.013
7. Dale T, Downs J, Wong K, Leonard H. The perceived effects of cannabis products in the management of seizures in CDKL5 deficiency disorder. Epilepsy Behav. 2021;122:108152. https://doi.org/10.1016/j.yebeh.2021.108152
8. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrel EC, Privitera M, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med. 2018;378:1888–97. https://doi.org/10.1056/NEJMoa1714631
9. Thiele EA, Bebin EM, Bhathal H, Jansen FE, Kotulska K, Lawson JA, et al. 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
10. Devinsky O, Verducci C, Thiele EA, Laux LC, PatelAD FF, SzaflarskiJP WA, et al. Open-label use of highlypurified 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
11. Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, et al. Cannabidiol in patients with treatment resistant epilepsy: an open-label interventional trial. Lancet Neurol. 2016;15(3):270–8.
12. Hurley EN, Ellaway CJ, Johnson AM, Truong L, Gordon R, Galettis P, et al. Efficacy and safety of cannabidivarin treatment of epilepsy in girls with Rett syndrome: a phase 1 clinical trial. Epilepsia. 2022;63(7):1736–47. https://doi.org/10.1111/epi.17247
13. Desnous B, Beretti T, Muller N, Neveu J, Villeneuve N, Lépine A, et al. Efficacy and tolerance of cannabidiol in the treatment of epilepsy in patients with Rett syndrome. Epilepsia Open. 2024;9(1):397–403. https://doi.org/10.1002/epi4.12796
14. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522–30. https://doi.org/10.1111/epi.13670
15. Lattanzi S, Trinka E, Striano P, Rocchi C, Salvemini S, Silvestrini M, et al. Highly purified cannabidiol for epilepsy treatment: a systematic review of epileptic conditions beyond Dravet syndrome and Lennox-Gastaut syndrome. CNS Drugs. 2021;35(3):265–81. https://doi.org/10.1007/s40263-021-00807-y
16. Tarquinio DC, Hou W, Berg A, Kaufmann WE, Lane JB, Skinner SA, et al. Longitudinal course of epilepsy in Rett syndrome and related disorders. Brain. 2017;140(2):306–18. https://doi.org/10.1093/brain/aww302
17. Peron A, Canevini MP, Ghelma F, Arancio R, Savini MN, Vignoli A. Phenotypes in adult patients with Rett syndrome: results of a 13-year experience and insights into healthcare transition. J Med Genet. 2022;59(1):39–45. https://doi.org/10.1136/jmedgenet-2020-107333
18. Vignoli A, Savini MN, Nowbut MS, Peron A, Turner K, La Briola F, et al. Effectiveness and tolerability of antiepileptic drugs in 104 girls with Rett syndrome. Epilepsy Behav. 2017;66:27–33. https://doi.org/10.1016/j.yebeh.2016.10.006
19. Glaze DG, Percy AK, Skinner S, Motil KJ, NeulJL BJO, Lane JB, et al. Epilepsy and the natural history of Rett syndrome. Neurology. 2010;74(11):909–12. https://doi.org/10.1212/WNL.0b013e3181d6b852
20. Pintaudi M, Calevo MG, Vignoli A, Baglietto MG, Hayek Y, Traverso M, et al. Antiepileptic drugs in Rett syndrome. Eur J Paediatr Neurol. 2015;19(4):446–52. https://doi.org/10.1016/j.ejpn.2015.02.007
21. Wong K, Junaid M, Alexander S, Olson HE, Pestana-Knight EM, Rajaraman RR, et al. Caregiver perspective of benefits and side effects of anti-seizure medications in CDKL5 deficiency disorder from an international database. CNS Drugs. 2024;38(9):719–32. https://doi.org/10.1007/s40263-024-01105-z
22. Knight EMP, Amin S, Bahi-Buisson N, Benke TA, Cross JH, Demarest ST, et al. Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2022;21(5):417–27. https://doi.org/10.1016/S1474-4422(22)00077-1
Erratum in: Lancet Neurol 2022;21(7):e7. https://doi.org/10.1016/S1474-4422(22)00230-7.
23. Olson HE, Amin S, Bahi-Buisson N, Devinsky O, Marsh ED, Pestana-Knight E, et al. Long-term treatment with ganaxolone for seizures associated with cyclin-dependent kinase-like 5 deficiency disorder: two-year open-label extension follow-up. Epilepsia. 2024;65(1):37–45. https://doi.org/10.1111/epi.17826
24. Gil-Nagel A, Cross JH, Devinsky O, Ceulemans B, Lagae L, Knupp K, et al. Comprehensive scoping review of fenfluramine's role in managing generalized tonic-clonic seizures in developmental and epileptic encephalopathies. Epilepsia. 2024;65(8):2186–99. https://doi.org/10.1111/epi.18020
25. Borowicz-Reutt K, Czernia J, Krawczyk M. CBD in the treatment of epilepsy. Molecules. 2024;29(9):1981. https://doi.org/10.3390/molecules29091981
26. Reyes Valenzuela G, Gallo A, Calvo A, Chacón S, Fasulo L, Galicchio S, et al. Purified cannabidiol as add-on therapy in children with treatment-resistant infantile epileptic spasms syndrome. Seizure. 2024;115:94–9. https://doi.org/10.1016/j.seizure.2024.01.010
27. Klein P, Tolbert D, Gidal BE. Drug-drug interactions and pharmacodynamics of concomitant clobazam and cannabidiol or stiripentol in refractory seizures. Epilepsy Behav. 2019;99:106459. https://doi.org/10.1016/j.yebeh.2019.106459

28. Tzadok M, Gur-Pollack R, Florh H, Michaeli Y, Gilboa T, Lezinger M, et al. Real-life experience with purified cannabidiol treatment for refractory epilepsy: a multicenter retrospective study. Pediatr Neurol. 2024;150:91–6. https://doi.org/10.1016/j.pediatrneurol.2023.10.012
29. Cerulli Irelli E, Mazzeo A, Caraballo RH, Perulli M, Moloney PB, Peña- Ceballos J, et al. Expanding the therapeutic role of highly purified cannabidiol in monogenic epilepsies: a multicenter real-world study. Epilepsia. 2025. https://doi.org/10.1111/epi.18378
30. Calvello C, Fernandes M, Lupo C, Placidi F, Izzi F, Bianco C, et al. Highly purified cannabidiol improves stability and postural tone in adult patients with Lennox-Gastaut syndrome: a case series. Epileptic Disord. 2023;25(1):74–9. https://doi.org/10.1002/epd2.20049
31. Ferrera G, Ricci E, Vignoli A, Savini MN, Viganò I, Chiesa V, et al. Highly purified cannabidiol in the treatment of drug-resistant epilepsies: a real-life impact on seizure frequency, quality of life, behavior, and sleep patterns from a single Italian center. Epilepsy Behav. 2023;147:109409. https://doi.org/10.1016/j.yebeh.2023.109409
32. Berg AT, Dixon-Salazar T, Meskis MA, Danese SR, Le NMD, Perry MS. Caregiver-reported outcomes with real-world use of cannabidiol in Lennox-Gastaut syndrome and Dravet syndrome from the BECOME survey. Epilepsy Res. 2024;200:107280. https://doi.org/10.1016/j.eplepsyres.2023.107280

How to cite this article: Vignoli A, Prato G, Alfei E, Bagnasco I, Danieli A, Celario M, et al. Is highly purified cannabidiol a treatment opportunity for drug-resistant epilepsy in subjects with typical Rett syndrome and CDKL5 deficiency disorder? Epilepsia Open. 2025;10:1111–1119. https://doi.org/10.1002/epi4.70078