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Real-world effectiveness and tolerability of cannabidiol in pediatric and adult patients with developmental and epileptic encephalopathies: a retrospective single-center study

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Abstract

Background

Developmental and epileptic encephalopathies (DEEs) are severe, drug-resistant epilepsies commonly associated with behavioral and cognitive impairment. Cannabidiol (CBD) is approved as adjunctive therapy for seizures associated with Dravet syndrome, Lennox–Gastaut syndrome, and tuberous sclerosis complex, but real-world evidence on outcomes beyond seizure control, and in patients treated outside these approved indications, remains limited. We performed a retrospective single-center study of pediatric and adult patients with DEEs who started adjunctive CBD between 2015 and 2025, to evaluate its real-world effectiveness and tolerability on seizure, behavioral, and cognitive outcomes at 3, 6, and 12 months.

Results

Fifty patients were included (mean age 22.1 ± 11.6 years; 58% female); 62% had combined focal and generalized seizures, and among generalized seizures, tonic–clonic seizures were the most frequent type (32%). A genetic etiology was identified in 48% of patients. Median monthly seizure frequency decreased from 31 at baseline to 16 at 6 months ($p = 0.005$) and 8 at 12 months ($p = 0.007$), and a ≥ 50% reduction in seizure frequency was achieved in 30.8%, 64.0%, and 48.0% of patients at 3, 6, and 12 months, respectively. Caregiver-reported behavioral improvement was noted in 34.8% and 33.3% of patients at 6 and 12 months, and cognitive improvement in 36.4% and 25.0%, respectively. At 6 months, cognitive improvement was associated with the absence of psychomotor delay ($p = 0.011$), a diagnosis of Dravet syndrome ($p = 0.036$), and lower intellectual disability severity ($p = 0.005$). Adverse events occurred in 50% of patients, most commonly somnolence; no serious adverse events were reported.

Conclusions

Adjunctive CBD was associated with a clinically meaningful reduction in seizure frequency, particularly for convulsive seizures. Improvements in behavioral and cognitive domains were observed in up to one-third of patients, supporting a broader clinical benefit beyond seizure control in this population.

Background

Developmental and epileptic encephalopathies (DEEs) comprise a heterogeneous group of severe disorders characterized by early-onset, drug-resistant epilepsy and progressive impairment of cognition, behavior, and adaptive functioning. In these disorders, epileptic activity itself, together with the underlying genetic or structural etiology, contributes to adverse neurodevelopmental outcomes, frequently associated with behavioral manifestations such as irritability, hyperactivity, sleep disorders,

autistic features, and aggressiveness (1, 2). Improving seizure control while minimizing cognitive and behavioral burden remains a major therapeutic challenge.

Among DEEs, Dravet syndrome (DS), Lennox–Gastaut syndrome (LGS), and tuberous sclerosis complex (TSC) represent some of the most studied conditions. DS, most commonly caused by pathogenic variants in *SCN1A* gene, is characterized by early-onset febrile and afebrile seizures, multiple seizure types, and significant neurodevelopmental and behavioral impairment (3). LGS is defined by multiple seizure types, particularly tonic and atonic seizures, a characteristic slow spike-and-wave electroencephalographic pattern, and intellectual disability (4). TSC is a multisystem genetic disorder resulting from mutations in *TSC1* or *TSC2*, and characterized by a high prevalence of epilepsy and frequent comorbidities, including different degrees of autism spectrum disorder and intellectual disability (5).

Cannabidiol (CBD), a non-psychoactive phytocannabinoid, has emerged as an important therapeutic option for treatment-resistant epilepsies. A purified oral formulation of cannabidiol was approved by the European Medicines Agency (EMA) as adjunctive therapy for seizures associated with DS and LGS in pediatric patients (from 2 years of age) with marketing authorization in 2019. Subsequently, the approval was expanded to include seizures associated with TSC, with the European Commission granting the indication for TSC in 2021(6).

Beyond its approved indications, CBD is increasingly prescribed off-label in rare and severe epileptic syndromes, particularly DEEs such as CDKL5 or SYNGAP1 encephalopathy. In these populations, evidence remains limited and largely based on observational studies (7). Moreover, in DEEs, therapeutic goals extend beyond seizure control to include behavior, alertness, sleep, and quality of life. (7, 8).

The antiseizure effects of CBD are mediated through mechanisms distinct from those of conventional antiseizure medications (ASMs) and are largely independent of classical cannabinoid receptors (9–12).

Given the expanding use of CBD in DEEs and the clinical relevance of behavioral outcomes in this population, further real-world evidence is needed to better characterize its impact beyond seizure control. With this study, we aim to evaluate the impact of CBD in DEEs population, not only on seizure response, but also including behavior and cognition benefits.

Methods

Study design and participants

This single-center retrospective study included pediatric and adult patients with DEE and drug resistant epilepsy who started CBD as an adjunctive antiseizure medication (ASM) between July 2015 and January 2025. All DEE patients were attended at a dedicated Epilepsy Unit of a tertiary hospital. This study was approved by the Clinical Research Ethics Committee (Comité de Ética de la Investigación con medicamentos, CEIm) of Vall d'Hebron University Hospital (PR(AG)94/2024).

CBD was initiated following a slow titration protocol to facilitate tolerability. The dose increased by 2.5mg/kg/day weekly, reaching 10mg/kg/day or up to 20mg/kg/day depending on clinical response and tolerability.

DEE diagnosis was established according to the former ILAE definition. All patients with a previously diagnosed DEE were reclassified according to this definition (1). Drug-resistant epilepsy was defined as failure to achieve sustained seizure freedom despite adequate trials of two appropriately chosen and tolerated ASMs, according to the ILAE task force criteria (13)

Data collection and follow up

We collected data on demographics, epilepsy characteristics, and comorbidities, including behavioural and cognitive features.

Regarding seizure characteristics, we included current seizure types, as well as monthly frequency based on caregiver-reported diaries. Seizure types were categorized as follows for subgroup analyses: seizures with prominent motor symptoms (tonic-clonic, tonic, atonic and myoclonic seizures) vs. seizures without prominent motor symptoms.

Intellectual disability was classified as mild, moderate, or severe based on the ability to perform various daily activities independently, as assessed during outpatient visits (14). Cognitive improvement was assessed based on subjective reports from the patient's family or caregiver as documented in the clinical records. A positive response was considered when caregivers consistently reported clinically meaningful improvements in cognitive performance, adaptive functioning, communication skills, social interaction, behavior, or autonomy in daily activities compared with the pre-treatment period.

Data were obtained from a structured database routinely used in the epilepsy outpatient clinics to systematically record clinical parameters at each visit. The clinical response in terms of seizure frequency, treatment-related adverse events (AEs) and cognitive/behavioral outcomes were assessed at baseline and at 3, 6, and 12 months follow up.

Data analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0. Categorical variables were reported as frequencies (percentages) and continuous variables as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate. Normality assumption of quantitative variables was checked with the use of quantile-quantile (Q-Q) plots.

Changes in seizure frequency during follow-up were assessed using the Wilcoxon signed-rank test. Associations between baseline clinical factors and outcomes (≥ 50% seizure reduction, cognitive and behavioral improvement, and AEs) were assessed by Pearson’s chi-square or Fisher’s exact test for

categorical variables, Student's t test for continuous variables and Mann-Whitney U test for quantitative variables without an approximately normal distribution.

CBD retention rates were analyzed with the Kaplan-Meier product limit survival method using the log-rank test to determine statistical significance between groups; associations with quantitative variables were assessed with simple Cox proportional hazard models.

A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 50 patients were included, the mean age at inclusion was 22.1 ± 11.6 years, and 58% were female. Regarding seizure semiology, 62% of patients presented with both focal and generalized seizures, 20% had exclusively focal seizures, and 18% had only generalized seizures. Among generalized seizures, tonic–clonic were the most frequent type (32%), followed by tonic (30%), atypical absence (16%), and atonic seizures (2%) (Table 1).

Table 1
Baseline demographic and clinical characteristics of the study population (N = 50).

Characteristic	Value
Age at CBD initiation, mean ± SD, years	22.1 ± 11.6
Female sex, n (%)	29 (58)
Age at epilepsy onset, median (IQR), years	0.0 (0.0–3.2)
Previous ASMs, median (IQR)	7 (5–9)
Concomitant ASMs, median (IQR)	3 (2–4)
Behavioral disorder, n (%)	26 (52)
Intellectual disability, n (%)	
Mild	6 (12)
Moderate	12 (24)
Severe	31 (62)
Epilepsy etiology, n (%)	
Genetic	24 (48)
Unknown	18 (36)
Structural	5 (10)
Metabolic	1 (2)
Autoimmune	1 (2)
Infectious	1 (2)
Confirmed genetic diagnosis, n (%)	19 (38)
Epilepsy type, n (%)	
Focal	10 (20)
Generalized	9 (18)
Combined focal and generalized	31 (62)
Seizure types, n (%)	
Focal impaired awareness seizures	29 (58)
Focal aware seizures	2 (4)
Focal motor seizures	26 (52)

Characteristic	Value
Focal non-motor seizures	8 (16)
Focal to bilateral tonic–clonic seizures	6 (12)
Generalized tonic–clonic seizures	16 (32)
Tonic seizures	15 (30)
Atypical absence seizures	8 (16)
Atonic seizures	1 (2)
Convulsive seizures, n (%)	38 (76)
Non-convulsive seizures, n (%)	26 (52)
Monthly total seizure frequency, median (IQR)	31 (11–69)
Monthly convulsive seizure frequency, median (IQR)	6 (0.75–30)
Monthly non-convulsive seizure frequency, median (IQR)	5 (0–30)
Baseline CBD dose, median (IQR), mg/kg/day	2.5 (2.0–2.5)
Most common concomitant ASMs, n (%)	
Clobazam	32 (64)
Valproate	26 (52)
Topiramate	12 (24)
Lacosamide	11 (22)
Lamotrigine	11 (22)

ASMs: antiseizure medications; CBD: cannabidiol; IQR: interquartile range.

A genetic etiology was presumed in 24 patients (48%), of whom 19 had a confirmed genetic diagnosis (Table 2). This was followed by unknown etiology (36%, n = 18) and structural causes (10%, n = 5). Less frequent etiologies included metabolic, infectious, and autoimmune causes, each accounting for one patient (2%).

Table 2
Genetic etiologies identified in the study cohort

Genetic diagnosis / condition	Gene	n	% of total cohort
Dravet syndrome	*SCN1A*	8	16.0
CDKL5 deficiency disorder	*CDKL5*	2	4.0
FOXG1-related encephalopathy	*FOXG1*	1	2.0
Band heterotopia	*EML1*	1	2.0
Tuberous sclerosis complex	*TSC2*	1	2.0
GAND syndrome	*GATAD2B*	1	2.0
Schaaf–Yang syndrome	*MAGEL2*	1	2.0
GRIA2-related epilepsy	*GRIA2*	1	2.0
RNU4-2-associated epilepsy	*RNU4-2*	1	2.0
Agyria-Pachuygyria encephalopathy	*Del Cr17p13.3 (includes gen PAFAH1B1)*	1	2.0
STXBP1-encephalopathy	*STXBP1*	1	2.0
Total (genetic diagnosis identified)		**19**	**38**

Intellectual disability was documented in 98% of the cohort and was classified as severe in 62%, moderate in 24%, and mild in 12% of cases. A behavioral disorder was reported in 52% of patients, most commonly of moderate severity (60%), followed by mild (28%) and severe (12%).

Prior to CBD initiation, patients had received a median of 7 (IQR 5–9) ASMs. At the time of CBD initiation, the median number of concomitant ASMs was 3 (IQR 2–4).

Response to treatment and associated factors:

Impact on seizure frequency:

Total monthly seizure frequency decreased from a median of 31 (IQR 11–69) to 16 (IQR 3–60) at 6 months (p = 0.005) and 8 (IQR 2–32) at 12 months follow up (p = 0.007). Median seizure reduction was − 4.1% (IQR − 56% to 0%) at 3 months, -70.0% (IQR − 90% to -5.6%) at 6 months, and − 40.0% (IQR − 95% to 0%) at 12 months (Table 2, Fig. 1). Convulsive seizures decreased significantly over follow-up, from a median of 6 (IQR 0.75–30) per month at baseline to 2 (IQR 0–14) at 6 months (p = 0.013) and 1 (IQR 0–9) at 12 months (p = 0.026).

Non-convulsive seizures showed a variable response, with reductions at 3 (p = 0.043) and 12 months (p = 0.028) but not at 6 months (Table 3).

Table 3
Clinical response to CBD over time

Variable	Baseline (n = 50)	3 months (n = 39)	6 months (n = 25)	12 months (n = 25)
CBD dose, mg/kg/day	2.5 (2–2.5)	10 (7–14)	10 (5–10)	10 (9–14)
Dose adjustment, n (%)	—	31 (83.8%)	16 (69.6%)	8 (32.0%)
Adverse events, n (%)	5 (10.6%)	15 (38.5%)	4 (16.0%)	3 (12.0%)
Cognitive improvement, n (%)	—	7 (18.4%)	8 (36.4%)	6 (25.0%)
Behavioral improvement, n (%)	—	7 (18.4%)	8 (34.8%)	8 (33.3%)
Seizure frequency (monthly)				
Total seizures	31 (11–69)	30 (4–61)*	16 (3–60)*	8 (2–32)*
Seizures with prominent motor symptoms	6 (0.75–30)	4 (0–20)*	2 (0–14)*	1 (0–9)*
Only convulsive (n = 38)	12 (4–45)	4 (1–30)*	4 (0–15)*	3 (0–12)*
Seizures without prominent motor symptoms	5 (0–30)	0 (0–30)*	0 (0–45)	0 (0–19)*
Only non-convulsive (n = 26)	30 (26–97)	30 (8–120)*	45 (1–90)	19 (1–60)*
Seizure freedom, n (%)	—	2 (5.1%)	3 (12.0%)	2 (8.0%)
≥ 50% seizure reduction, n (%)	—	12 (30.8%)	16 (64.0%)	12 (48.0%)
Median percentage seizure reduction (IQR) (%)	—	−4.1% (− 56 to 0)	−70.0% (− 90 to − 5.6)	−40.0% (− 95 to 0)

Data are presented as median (IQR) or n (%). Sample size varies across timepoints due to treatment discontinuation and loss to follow-up. Adverse events are reported per visit; overall incidence during follow-up was 50%. Subgroups (only convulsive / only non-convulsive) are not mutually exclusive.

**p < 0.05 comparing to baseline values.*

Seizure freedom was achieved in 2/39 (5.1%) of patients at 3 months, 3/25 (12.0%) at 6 months, and 2/25 (8.0%) at 12 months. A ≥ 50% reduction in seizure frequency was observed in 12/39 (30.8%) of patients at 3 months, 16/25 (64.0%) at 6 months, and 12/25 (48.0%) at 12 months.

At 3 months, younger age (mean 12.8 vs 24.2, p = 0.003) and higher baseline seizure frequency (median 60 vs 30, p = 0.016) were associated with ≥ 50% reduction. At 6 months, generalized seizure type (90.9%

for tonic-clonic vs 71.4% for tonic vs 0% for absence seizures, p = 0.023) and the presence of convulsive seizures (75.0% vs. 20%, p = 0.040) were associated with a higher response rate.

At 12 months, concomitant use of TPM showed a trend toward poorer response to CBD (14.3% vs 61.1%, p = 0.073). No associations between clinical outcomes and the use of other ASM were observed.

50% of patients experienced AEs, most commonly somnolence (30%), followed by irritability (8%) and gastrointestinal symptoms (8%). AEs were more frequent at 3 months (38.5%) and decreased at 6 (16.0%) and 12 months (12.0%). No serious AEs were reported.

CBD was discontinued in 50% of patients during the first year, mainly due to combined lack of efficacy and AEs (36.0%), AEs alone (28.0%), or lack of efficacy (24.0%). Median time to discontinuation was 4.1 months.

Retention rates were 80.0% at 3 months, 70.0% at 6 months, and 53.4% at 12 months. No baseline factors were associated with AEs or treatment withdrawal.

Non-seizure comorbidities:

Behavioral improvement was reported in 18.4% of patients at 3 months, 34.8% at 6 months, and 33.3% at 12 months.

Cognitive improvement was observed in 18.4% of patients at 3 months, 36.4% at 6 months, and 25.0% at 12 months. At 3 months, younger age (mean 10.0 vs 22.3, p = 0.017), fewer concomitant ASMs (median 2 vs 3, p = 0.034), and lower intellectual disability (50% for mild vs 37.5% for moderate, and 7.7% for severe, p = 0.013) were associated with higher improvement (Fig. 2). At 6 months, absence of psychomotor delay (83.3% vs 18.8%, p = 0.011), DS (100% vs 26.3%, p = 0.036), and lower intellectual disability (100% for mild vs 71.4% for moderate, and 14.3% for severe, p = 0.005) were associated with improvement. At 12 months, younger age (mean 10.0 vs 22.3, p = 0.028), earlier epilepsy onset (median 0 vs 1 year, p = 0.048), and absence of psychomotor delay (66.7% vs 11.1%, p = 0.018) were associated with a higher improvement.

Discussion

This real-world study evaluates the effect of CBD in a pediatric and adult population with DEEs, focusing not only on seizure response but also on behavioral and cognitive outcomes. The key findings include a significant reduction in seizure frequency considering the refractoriness of these patients, together with a positive impact extending beyond seizure control.

Add-on CBD was associated with a meaningful reduction in seizure frequency, with the greatest effect observed at 6 months and a sustained clinical response at 12 months. This pattern is consistent with randomized controlled trials and open-label extension studies reporting significant seizure reduction in

DS and LGS (15–19). In our study, seizure response did not differ according to etiology, supporting the rationale for extending CBD to DEEs beyond the currently approved indications. Unlike these trials, our real-world design reflects routine clinical practice more closely.

The reduction was more pronounced for convulsive seizures, in line with previous real-world studies (20), this is particularly relevant given their greater impact on patient safety and quality of life. No differences were observed for non-convulsive seizures, which may partly reflect the difficulty of identifying and quantifying these events in patients with severe neurodevelopmental impairment.

Behavioral improvement was observed in approximately one-third of patients and remained stable over time. Behavioral disorders, including irritability, hyperactivity, and sleep-related difficulties are a major contributor to disease burden and caregiver stress, sometimes exceeding the impact of seizure frequency itself. Improvement in this domain is clinically meaningful even in patients with only partial seizure control, consistent with prior randomized clinical trials and real-world studies, reporting benefits in behavior, sleep, and quality of life (15–17, 21, 22). These findings suggest that CBD may exert broader neuromodulatory effects beyond its antiseizure properties, even when seizure reduction is modest.

Behavioral improvement was more frequent in patients with moderate disability than in those with severe impairment, suggesting a possible window of responsiveness. The underlying mechanisms remain unclear, but may combine direct central effects of CBD, potentially mediated via endocannabinoid, serotonergic, or GABAergic pathways, with indirect effects related to seizure reduction or improved sleep. (23, 24)

As with seizure response, no differences in behavioral response were observed across etiological subgroups. Although limited by sample size, this is consistent with recent real-world evidence reporting benefit across multiple monogenic epilepsies and DEEs (20), supporting the concept that both seizure and non-seizure outcomes may improve regardless of genetic diagnosis. Our results reinforce the potential benefit across a broader range of DEEs beyond currently approved indications.

Cognitive outcomes followed a similar trajectory, with a peak improvement at 6 months. Improvement was associated with younger age, absence of psychomotor delay, and DS, consistent with prior reports (7, 22, 25, 26) However, the variability observed underscores the heterogeneity of DEEs and the challenges of detecting meaningful changes in cognitive function in this population.

The attenuation of response at 12 months and a discontinuation rate of approximately 50% highlight the need for longer follow-up. Treatment retention in our cohort was lower than that reported in both long-term expanded access programs and other real-world studies (7, 27, 28), which may reflect differences in patient selection and clinical characteristics. Unlike many previous cohorts focused on approved indications such as Dravet syndrome and Lennox-Gastaut syndrome, our study included a broader spectrum of developmental and epileptic encephalopathies, reflecting routine clinical practice but potentially contributing to lower long-term treatment retention.. Moreover, treatment retention should be interpreted as a composite outcome reflecting both effectiveness and tolerability, as discontinuation in

routine clinical practice is frequently driven by insufficient perceived benefit in addition to adverse events. Further studies evaluating the impact of drug-drug interactions, treatment accessibility, and economic factors on long-term retention are warranted.

CBD was generally well tolerated, with no severe AEs. AEs were more common early in treatment and contributed to discontinuation in some patients, consistent with clinical trials and real-world data. Careful dose titration and close monitoring, particularly at initiation, may improve tolerability and treatment adherence (7, 27–29).

Taken together, these findings support the systematic assessment of behavioural and cognitive domains, in addition to seizure frequency, when evaluating CBD response in clinical practice, since improvements in these domains may occur independently of, and provide additional value beyond seizure control alone.

This study has several limitations. First, the retrospective design and lack of standardized assessment tools, particularly for behavioral and cognitive outcomes, meant that improvements were based on clinical judgment and caregiver reports. Although highly relevant to routine practice, this introduces subjectivity and limits comparability across studies, reflecting a broader challenge in the field, where non-seizure outcomes remain insufficiently captured despite their clinical importance. Second, the progressive reduction in sample size over follow-up, driven mainly by treatment discontinuation, may introduce a survivorship bias, as patients remaining in the cohort at later time points could represent a subgroup with a more favorable response to CBD. Third, this was a single-center study without a control group, which may limit the generalizability of our findings.

Conclusions

CBD was associated with a meaningful reduction in seizure frequency in both pediatric and adult patients across a broad range of DEEs, with a particularly notable effect on convulsive seizures. Importantly, CBD was also associated with improvements in behavior and cognition representing a clinically meaningful benefit that may positively impact patients' quality of life.

Careful dose titration and close follow-up may help improve treatment adherence. Future studies incorporating standardized and multidimensional outcome measures are needed to further characterize the full clinical impact of CBD.

Abbreviations

AE
adverse event
ASM
antiseizure medication
CBD

cannabidiol
CI
confidence interval
DEE
developmental and epileptic encephalopathy
DS
Dravet syndrome
EMA
European Medicines Agency
IQR
interquartile range
LGS
Lennox–Gastaut syndrome
SD
standard deviation
TSC
tuberous sclerosis complex.

Declarations

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee (Comité de Ética de la Investigación con medicamentos, CEIm) of Vall d'Hebron University Hospital (PR(AG)94/2024) and was conducted in accordance with the Declaration of Helsinki. Given the retrospective design of the study, the requirement for individual informed consent was waived by the ethics committee.

Consent for publication

Not applicable.

Competing interests

COI disclosure: Elena Fonseca declares consulting honoraria from UCB, Jazz Pharmaceuticals and Angelini Pharma, and speaker fees, research funding, and travel support from UCB, Esteve, Eisai Inc., BIAL, Jazz Pharmaceuticals, Angelini Pharma, and Sanofi Genzyme. Laura Abraira declares consulting honoraria from Jazz Pharmaceuticals and Angelini Pharma, and speaker fees, research funding, and travel support from UCB, Esteve, Eisai Inc., BIAL, Jazz Pharmaceuticals, Angelini Pharma, and Sanofi Genzyme. M. Toledo has received research funding and speaking fees from UCB Pharma, Angelini, Arvelle, Jazz Pharma, BIAL Pharmaceutical, EISAI Inc and Esteve Laboratorios. E. Santamarina has received research funding and speaking fees from UCB Pharma, BIAL Pharmaceutical, EISAI Inc and

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Author Contribution

T.J and L.A designed the study, collected the data and wrote the main manuscript text and prepared the figuresI.P helped collect the dataM.Q did the statystical analysis and wrote the methodology on the mansucript textAll other authors reviewed the manuscript

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Data Availability

All data supporting the findings of this study are available within the paper. For supplementary information you can contact the corresponding author

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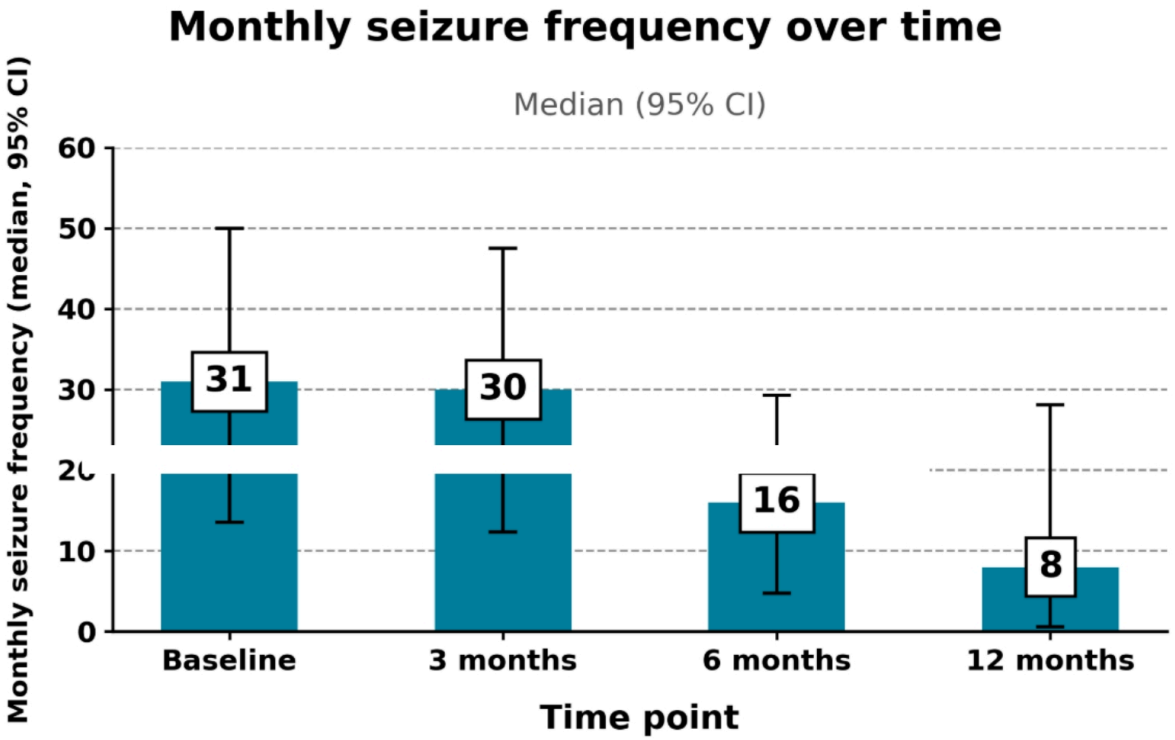
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Figures



CI, confidence interval.
Monthly seizure frequency represents the total number of seizures per month.

Figure 1

Bar chart showing the reduction in seizures at 3, 6, and 12 months after initiation of cannabidiol treatment.

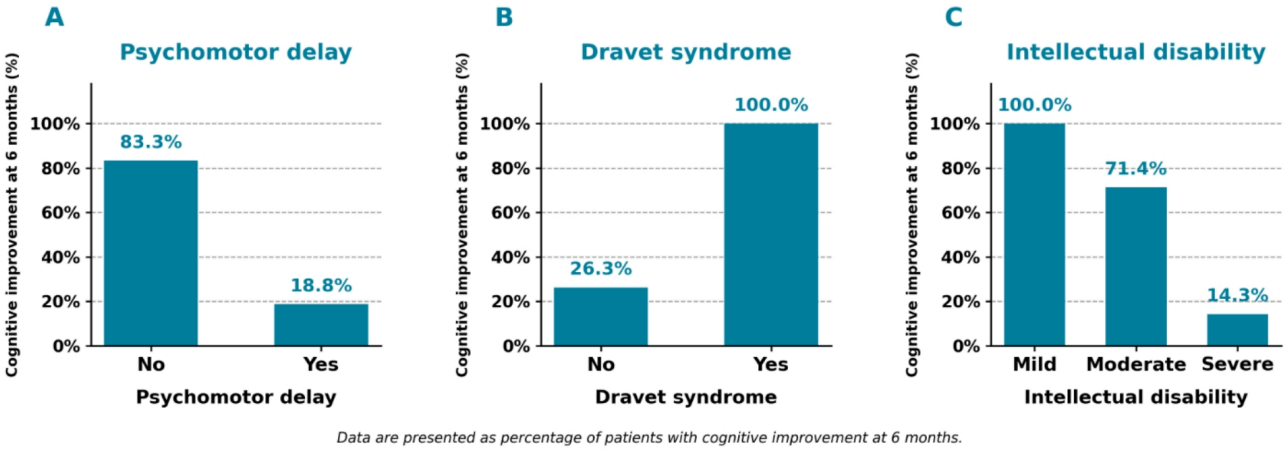


Figure 2

Bar charts showing the association between cognitive improvement and psychomotor delay (2A), Dravet syndrome (2B), and intellectual disability (2C)