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ORIGINAL RESEARCH ARTICLE

Long-Term Safety, Tolerability, and Efficacy of Cannabidiol in Children with Refractory Epilepsy: Results from an Expanded Access Program in the US

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Abstract

Background Purified cannabidiol is a new antiepileptic drug that has recently been approved for use in patients with Lennox–Gastaut and Dravet syndromes, but most published studies have not extended beyond 12–16 weeks.

Objective The objective of this study was to evaluate the long-term safety, tolerability, and efficacy of cannabidiol in children with epilepsy.

Methods Patients aged 1–17 years with refractory epilepsy were enrolled in an open-label prospective study through individual patient and expanded access programs between April 2013 and December 2014. Seizure types were video-electroencephalogram confirmed prior to enrollment. After a 28-day evaluation period, during which baseline seizure frequency was assessed, cannabidiol was given as add-on therapy at 5 mg/kg/day and titrated weekly by 5-mg/kg increments to a dose of 25 mg/kg/day. Blood tests were performed at baseline, after 1, 2, and 3 months, and every 3 months thereafter. Trough concentrations of concomitant antiepileptic drugs were measured at baseline, after 1, 2, and 3 months of therapy, and as clinically indicated afterwards. Concomitant antiepileptic drugs, ketogenic diet ratio, and vagal nerve stimulator settings remained unchanged during the baseline period and the first 3 months of treatment, unless there was a significant increase in plasma concentrations. Seizure frequency was reported daily in seizure diaries by parents or caregivers. Clinical assessments occurred after 15 days of treatment, at 1 month, at 3 months, and every 3 months thereafter. Diaries of seizure frequency and adverse events were reviewed at each visit. The primary efficacy outcome was a reduction in seizure frequency and responders were defined as those patients achieving a > 50% reduction in motor seizures.

Results Twenty-six children were enrolled. Most had genetic epilepsies with daily or weekly seizures and multiple seizure types. All were refractory to prior antiepileptic drugs (range 4–11, mean 7), and were taking two antiepileptic drugs on average. Duration of therapy ranged from 4 to 53 months (mean 21 months). Adverse events were reported in 21 patients (80.8%), including reduced appetite in ten (38.4%), diarrhea in nine (34.6%), and weight loss in eight (30.7%). Four (15.4%) had changes in antiepileptic drug concentrations and three had elevated aspartate aminotransferase and alanine aminotransferase levels when cannabidiol was administered together with valproate. Serious adverse events, reported in six patients (23.1%), included status epilepticus in three, catatonia in two, and hypoalbuminemia in one. Fifteen patients (57.7%) discontinued cannabidiol for lack of efficacy, one because of status epilepticus, and one for severe weight loss. The retention rate declined rapidly in the first 6 months and more gradually thereafter. At 24 months, the number of patients continuing cannabidiol as adjunctive therapy was nine of the original 26 (34.6%). Of these patients, seven (26.9%) had a sustained > 50% reduction in motor seizures, including three (11.5%) who remain seizure free.

Conclusion Over a 4-year period, cannabidiol was effective in 26.9% of children with otherwise refractory epilepsy. It was well tolerated in about 20% of patients, but 80.8% had adverse events, including 23.1% with serious adverse events. Decreased appetite and diarrhea were frequent along with weight loss that became evident only later in the treatment.

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Key Points

Clinically meaningful improvement in seizure frequency (> 50% reduction) was sustained over 2–4 years in 7/26 (26.9%) of children with otherwise medically refractory epilepsy of various types, including three (11.5%) who became seizure free.

Most patients discontinued cannabidiol because of inefficacy, the majority doing so by 6 months. The retention rate at 2 years was 34.6% (9/26).

Adverse events were reported in 21/26 (80.8%) of children with decreased appetite, diarrhea, and weight loss being the most common. Serious adverse events were reported in 6/26 (23.1%) of the cohort.

Weight loss emerged only after several months on treatment, was clinically significant in 8/26 (30.7%) of patients, and resolved with dose reduction or treatment cessation.

1 Introduction

New safe and effective treatments are much needed for medically refractory epilepsy, particularly epileptic encephalopathies and severe epilepsy syndromes in children. Cannabidiol (CBD) is a non-psychoactive derivative of *Cannabis sativa* with anti-convulsant properties [1]. The short-term safety and efficacy of the pharmaceutical formulation of purified CBD (Epidiolex®; GW Pharmaceuticals, Cambridge, UK) has been studied in an open-label trial in children and young adults with refractory epilepsy [2], as well as in randomized trials in patients with Dravet syndrome and Lennox–Gastaut syndrome [3, 4], leading to US Food and Drug Administration approval in 2018 for use in these two conditions. However, only recently have data on long-term outcomes been published [5]. We report the long-term safety and efficacy of CBD as adjunctive therapy in a cohort of children with treatment-resistant epilepsy from the first center to administer CBD to patients with epilepsy, starting in 2013.

2 Methods

2.1 Study Subjects

Twenty-six patients aged 1–17 years with medically refractory epilepsy were enrolled under Food and Drug Administration-approved single-patient and expanded-access Investigational New Drug programs for treatment with a pharmaceutical grade plant-derived preparation of CBD as an add-on antiepileptic drug (AED). The first patient was enrolled as early as May 2013, but the majority were enrolled between January 2014 and December 2014. Short-term data have been previously reported as part of a prospective, open-label, expanded-access multicenter study [2], but the long-term data from this cohort have not been yet reported.

2.2 Study Drug and Concomitant Treatment

Cannabidiol as a 100-mg/mL sesame oil-based solution (Epidiolex®) was given as add-on therapy, titrated weekly from a starting dose of 5 mg/kg/day by 5-mg/kg increments to a target dose of 25 mg/kg/day. The doses of concomitant AEDs, ketogenic diet ratios, and vagal nerve stimulator settings remained unchanged during the preceding 4-week baseline period and first 3 months of treatment, unless there was a significant increase in plasma concentrations. Subsequently, doses could be adjusted to maximize seizure control and for adverse events (AEs). The study drug was provided at each visit and compliance with the study protocol was a requirement to continue the therapy.

2.3 Assessments

Seizure types in our cohort were video-electroencephalogram (EEG) confirmed prior to enrollment. Seizures were identified and recorded by the patient's parents or caregivers during the baseline assessment and throughout the treatment period. Daily diaries of seizure frequency and AEs were reviewed at each visit. Clinical assessment and laboratory testing, including complete blood count and liver function tests, were performed at baseline and repeated every 3 months to evaluate tolerability and efficacy. Trough concentrations of concomitant AEDs were performed at baseline, after 1, 2, and 3 months of therapy, and as clinically indicated afterwards. Compliance with seizure diaries, blood tests, and follow-up appointments was required to continue the treatment. The emergence of AEs was addressed by dose reduction or cessation of therapy. Responders were defined as those patients achieving a > 50% reduction in motor seizures, defined as seizures with tonic, clonic, and atonic components, as well as focal motor seizures and myoclonic absences. Myoclonic jerks were reported as present or absent and not quantified. In two patients with epilepsy with myoclonic absences, complete freedom from myoclonic absences was confirmed with a 24-h video-EEG with hyperventilation and photic stimulation.

3 Results

3.1 Clinical Features

Cohort characteristics are provided in Table 1. The 26 patients had a mean age of 9 years, and 13 (50%) were

Table 1 Clinical features of a cohort of pediatric patients receving cannabidiol (CBD) adjunctive therapy

Feature	Study subjects ($n=26$)
Female sex, *n* (%)	13 (50)
Age of seizure onset, y, range (mean)	Birth to 8 (1.5)
Age at enrollment, y, range (mean)	1–17 (9)
Number of AEDs trialed, range (mean)	4–11 (7)
Concurrent therapies	
Number of AEDs, range (mean)	0–3 (2)
Ketogenic diet, *n* (%)	4 (15)
Vagal nerve stimulator, *n* (%)	5 (19)
Duration of CBD treatment, mo, range (mean)	4–53 (21.8)
Epilepsy syndrome, *n* (%)	
Dravet syndrome	6 (23)
Epilepsy with myoclonic-absences	5 (19)
CDKL5 epileptic encephalopathy	5 (19)
Lennox–Gastaut syndrome	4 (15)
Other	6 (23)
Seizure types, *n* (%)	
Generalized tonic–clonic	16 (61.5)
Tonic	6 (23)
Myoclonic jerks	5 (19)
Myoclonic-absences	5 (19)
Hypermotor tonic spasms	5 (19)
Focal motor	3 (11.5)
Focal with generalization	2 (7.7)
Atypical absence	2 (7.7)
Tonic-atonic	1 (3.8)

AEDs antiepileptic drugs

female. Most patients had confirmed genetic epilepsies with frequent seizures, ranging from one per week to multiple per day, and often more than one seizure type. The most common diagnoses were Dravet syndrome [DS] (6, 23%), *CDKL5* encephalopathy (5, 19%), epilepsy with myoclonic absences [EMA] (5, 19%), and Lennox–Gastaut syndrome (4, 15%). Seizures had been refractory to several AEDs in all patients (range 4–11, mean 7), and patients were taking an average of two AEDs at the time of enrollment. The duration of CBD therapy ranged from 4 to 53 months (mean 21 months). All patients were treated with CBD as add-on therapy, but one patient (case 00) was transitioned to CBD monotherapy for 19 months, after which valproic acid (VPA) was added as clinically indicated. Details of individual patient characteristics, including genotypes, are provided in Table 2.

3.2 Adverse Events

Most patients (21/26, 80.8%) had at least one AE during treatment (Table 3). Reduced appetite (10, 38.4%), diarrhea (9, 34.6%), and clinically significant weight loss (8, 30.7%) were the most frequent AEs. While reduced appetite and diarrhea became apparent within the first 3 months of treatment, weight loss became evident typically only after at least 6 months. While weight loss or stagnation of weight gain resulting in a change in the weight percentile was considered clinically significant in eight patients (Fig. 1), some degree of weight loss was seen almost universally across the cohort [Table 1 of the Electronic Supplementary Material (ESM)]. In patients for whom weight loss was clinically significant, dose reduction typically led to stabilization and discontinuation of CBD was followed by weight gain (Fig. 1).

Four subjects (15.4%) had changes in trough plasma concentrations of concomitant AEDs during the titration of CBD requiring dose adjustment. Concentrations of clobazam (CLB) increased in three patients during the first 3 months of treatment: 600–790 ng/mL (case 02), 79–110 ng/mL (case 08), and 89–240 ng/mL (case 09). Increased CLB concentrations were associated with behavioral changes including aggression as previously observed in the same patient when taking high-dose CLB. In patients 02 and 08, increased CLB concentrations were asymptomatic. In another patient (case 20), phenobarbital concentrations increased from 43 to 55 mg/L and bromide concentrations increased from 140 to 170 mg/dL during CBD titration paralleling the increase of the CBD dose. Following introduction of VPA, while taking CBD, three patients developed elevated aspartate aminotransferase and alanine aminotransferase levels, which normalized with CBD dose reduction from 25 to 20, 15, and 9 mg/kg/day respectively.

Serious AEs included status epilepticus (3/26), leading to cessation of therapy in one patient (case 02), in whom the seizure increase paralleled the increase in the CBD dose and CBD was therefore deemed responsible. Another child discontinued CBD because of severe weight loss (− 16.6% of baseline), which persisted despite a dose decrease (case 10, Fig. 1, Table 1 of the ESM). Transient hypoalbuminemia was documented in one patient.

Catatonic psychosis emerged in two patients (cases 04 and 18). Symptoms in patient 04 with DS included echolalia, mumbling/talking to self or to a non-existing person, perseveration, and reduced environmental responsivity with a Bush–Francis catatonia rating scale score calculated at 22/69 (moderate/severe). Patient 18 with Lennox–Gastaut syndrome developed prolonged periods of reduced environmental responsivity, stereotypies, mutism, and paucity of spontaneous movements. For patient 18, these symptoms resolved upon discontinuation of CBD. In patient 04, who was seizure free taking CBD, the catatonia persisted, as attempts to reduce CBD below 12 mg/kg/day led to the recurrence of clusters of generalized tonic–clonic seizures. The EEGs in these patients ruled out the presence of nonconvulsive status epilepticus. In the seizure-free patient with

Table 2 Patient characteristics across the cohort of pediatric patients receiving cannabidiol (CBD) adjunctive therapy

Case	Age, sex	Age at onset	Epilepsy	Etiology	Prior treatments	Concurrent treatments	Seizure types	Baseline frequency	>50% response to CBD	Duration of CBD, mo	Adverse event	Treatment course and outcomes
0	11 y, M	4 y	EMA	Presumed genetic	ETZ, FBM, IVIg, KD, LTG, LZP, MTZ, CS, TPM, VPA, ZNS	CLB	MA GTC*	100/d Absent	Yes Yes	53	Decreased appetite Weight loss Elevated AST and ALT	90% reduction in MA CLB weaned off CBD monotherapy for 19 mo Onset of GTC at age 14 y VPA added with elevation in AST and ALT CBD dose reduced (9 mg/kg/d) and AST and ALT normalized Seizurefree on VPA and CBD for last 24 mo
1	5 y, F	9 mo	DS	*SCN1A* c.1028G > A p.G343D	OXC, STP, VPA	CLB, LEV, TPM	GTC MJ AA*	17/mo Present Absent	Yes No No	44	None	75% reduction in GTC with addition of CBD (20 mg/kg/d) to CLB, LEV, and TPM MJ with no response to CBD AA onset at age 6 y with no response to CBD
2	3 y, M	8 y	DS	*SCN1A* c.4462C > T p.Q1488X	LEV, PB	CLB, STP	GTC	16/mo	No	4	SE Explosive diarrhea Increased CLB concentration	CLB trough increased from 600 to 790 ng/mL at 1 mo CLB dose reduced SE attributed to CBD led to discontinuation of CBD after 4 mo
3	17 y, M	5 y	EMA	Presumed genetic	ACZ, ETZ, LEV, LTG, TPM, VPA, ZNS	CLB	MA GTC	40/d 2/y	No No	6	Decreased appetite Loose stool	CBD discontinued after 6 mo for inefficacy
4	12 y, F	6 mo	DS	*SCN1A* c.2589 + 3A > T	CBZ, LCM, LEV, OXC, PHT, ZNS	CLN, PB, TPM	GTC	103/mo	Yes	44	Explosive diarrhea Decreased appetite Weight loss Catatonia	CBD reduced to 20 mg/kg/d with resolution of diarrhea CBD reduced to 15 mg/kg/d for weight loss CBD reduced to 12 mg/kg/d for catatonic psychosis Seizure free on CBD, CLN, PB, and TPM Attempts to decrease any of these AEDs led to seizure recurrence

Table 2 (continued)

Case	Age, sex	Age at onset	Epilepsy	Etiology	Prior treatments	Concurrent treatments	Seizure types	Baseline frequency	>50% response to CBD	Duration of CBD, mo	Adverse event	Treatment course and outcomes
5	10 y, F	<1 wk	EMA	*SLC13A5* 1. c.655G > A p.G219R 2. c.1475T > C p.L492P	B6, CBZ, CLN, IVIg, KD, LEV, LTG, OXC, P5P, PB, PHT, TPM, VPA	ACZ, FBM	MA	100/d	No	5	Decreased appetite Food aversion	CBD reduced to 20 mg/kg/d for lack of appetite CBD discontinued after 5 mo for inefficacy
6	14 y, M	18 mo	EMA	Presumed genetic	ETZ, CBZ, KD, LCM, PB, TPM, VPA, ZNS	LTG, LEV	MA GTC	75/d 9/y	Yes Yes	43	Weight loss Elevated AST and ALT	>75% reduction in MA on CBD, LTG, and LEV, no response with GTCs LTG and LEV weaned off VPA added with elevation in AST and ALT CBD dose reduced to 15 mg/kg/d and AST and ALT normalized Seizure free on VPA and CBD (15 mg/kg/d)
7	5 y, M	22 mo	GE	Presumed genetic	ETZ, KD, LEV, OXC	CLB, CS	GTC Tonic	31/mo 3/mo	Yes Yes	43	Weight loss Decreased appetite Diarrhea Elevated AST and ALT	50% seizure reduction on FBM, VPA, and CBD (20 mg/kg/d) CLB and CS weaned off
8	3 y, F	5 wk	CDKL5 EE	*CDKL5* c.145 + 1G > A	LEV, LTG, OXC, PB, RUF, TPM, VPA, ZNS	CLB	HTS Tonic MJ	70/mo 70/mo Present	No No No	8	Increased CLB concentration Weight loss Increased seizures	CLB trough increased from 79 to 110 ng/mL Seizures increased beyond baseline CBD discontinued after 8 mo for inefficacy
9	6 y, F	2.5 y	EMA	Presumed genetic	Amantadine, ACZ, CLN, KD, LEV, LTG, MTZ, PB, VPA, ZNS	ETZ, CLB	MA	150/d	No	5	Lethargy Increased CLB concentration Decreased appetite	CLB trough increased from 89 to 240 ng/mL CLB dose reduced CBD discontinued after 5 mo for inefficacy
10	11 y, M	3 wk	CDKL5 EE	*CDKL5* c.1675 C > T p.R559X	ACTH, CLB, LEV, LTG, PB, TPM, VPA, ZNS	CLN, RUF, VGB, VNS	HTS	140/mo	No	21	Severe weight loss Sleepiness Loose stools	CBD reduced to 20 mg/kg/d at 12 mo and to 15 mg/kg/d at 20 mo CBD discontinued at 21 mo because of progressive weight loss

Table 2 (continued)

Case	Age, sex	Age at onset	Epilepsy	Etiology	Prior treatments	Concurrent treatments	Seizure types	Baseline frequency	>50% response to CBD	Duration of CBD, mo	Adverse event	Treatment course and outcomes
11	12 y, F	3.5 y	FE	Suspected vasculitis	CS, FBM, KD, LCM, LEV, LTG, OXC, PB, VPA	CLB, TPM, VNS	SG	25/mo	Yes	40	None	< 75% seizure reduction with addition of CBD to CLB, TPM, and VNS
12	7 y, M	3 mo	SCN8A EE	*SCN8A* c.706 + 173T > C	KD, LEV, LTG, OXC, PB, VPA	CLB, FBM, TPM, VNS	GTC	305/mo	No	25	Drowsiness Somnolence	CBD reduced to 15 mg/kg/d from month 9 for drowsiness/somnolence Diagnosed at age 8 y with SCN8A EE CBD was discontinued for inefficacy PHT added with > 50% seizure reduction
13	10 y, F	5 mo	DS	*SCN1A* p.F312S	CLB, LEV, STP, TPM, VPA, ZNS	KD	GTC MJ AA	21/mo Multiple daily Several daily	No No No	5	Decreased appetite Nausea Increased anxiety Insomnia	CBD discontinued after 5 mo for inefficacy
14	13 y, F	6 mo	DS	*SCN1A* c.4385_4389del p.Y1462CfsX27	CLN, FBM, KD, LEV, LTG, STP, TPM, verapamil, VPA, ZNS	CLB, VNS	GTC	10/mo	No	40	None	< 50% reduction on addition of CBD (23 mg/kg/d) to CLB and VNS
15	7 y, M	2.5 y	LGS	Unknown	CLN, FBM, LEV, OXC, TPM, verapamil, VPA	CLN	GTC	21/mo	No	17	None	CBD discontinued after 17 mo for inefficacy
16	6 y, F	4 mo	DS	*SCN1A* c.4911-3del p.D1637Del	LEV, LTG, PB, TPM	CLN, VPA	GTC MJ	5/mo 240/d	No No	16	Hypoalbuminemia Weight loss Decreased appetite Somnolence	Transient hypoalbuminemia (albumin of 2.1) after 10 mo of therapy CBD discontinued after 16 mo for inefficacy
17	15 y, F	5.5 y	FE	Unknown	LEV, LTG, PB, PHT, VPA	OXC, VGB	FM SG	21/mo 2/mo	No No	5	Daily diarrhea	CBD discontinued after 5 mo for inefficacy

Table 2 (continued)

Case	Age, sex	Age at onset	Epilepsy	Etiology	Prior treatments	Concurrent treatments	Seizure types	Baseline frequency	>50% response to CBD	Duration of CBD, mo	Adverse event	Treatment course and outcomes
18	10 y, M	2.5 y	LGS	Unknown	LEV, LTG	CBZ, FBM, TPM	GTC Tonic	1/mo 13/mo	No No	25	Explosive diarrhea Lack of appetite Weight loss SE Catatonia	CBD reduced to 15 mg/kg/d for diarrhea and weight less with resolution of diarrhea Developed catatonia after 7 mo CBD discontinued after 25 mo for inefficacy
19	4 y, F	3 wk	CDKL5 EE	*CDKL5* c.2047-2A > G	CLB, LEV, OXC, PB, TPM	CLN	HTS	85/mo	Yes	36	None	> 50% seizure reduction on addition of CBD (19 mg/kg/d) to CLN
20	22 mo, M	1 d	EIMFS	*KCNT1* c.776C > A p.A259D	B6, CLB, CLN, folinic acid, LEV, PHT, TPM	PB, KBr	Focal	34/d	No	6	Incease PB concentration Increased KBr concentration Intermittent vomiting	PB trough increased from 43 to 55 mg/L PB dose reduced CBD discontinued after 6 mo for inefficacy
21	1 y, M	1.5 wk	CDKL5 EE	*CDKL5* c.532C > T p.R178 W	ACTH, CLB, PB, TPM	KD, VGB	HTS FM*	27/d	No	23	SE Decreased appetite	Initial seizure freedom for 3 mo on CBD, VGB, and KD KD discontinued Isolated episode of focal SE with acute otitis media at age 2 y not attributed to CBD CBD discontinued after 23 mo for inefficacy
22	7 y, F	6 wk	CDKL5 EE	*CDKL5* c.1446delC p.Y482X	CBZ, OXC, PB, PHT, ZNS	CLN, KD, LTG, LEV	HTS MJ	125/mo Present	No No	9	Increased seizures Diarrhea Agitation	CBD reduced to 15 mg/kg/d for adverse events CBD discontinued after 9 mo for inefficacy
23	14 y, M	9 y	LGS	Unknown	LEV, LTG, OXC, VPA	LCM, OXC, TPM, VNS	GTC Tonic TA	1/mo 99/mo 16/mo	No No No	5	Increased seizures	CBD reduced to 20 mg/kg/d at 4 mo CBD discontinued after 5 mo for inefficacy
24	12 y, F	3 y	Rett syndrome	*MECP2* c.502C > T p.R168X	VNS, VPA	CLB, KD, OXC, TPM	GTC Tonic	2/mo 18/mo	No No	6	Severe agitation Insomnia Leg cramping	CBD reduced to 15 mg/kg/d for side effects CBD discontinued after 6 mo for inefficacy
25	12 y, M	4 y	LGS	Unknown	FBM, KD, LEV, LTG, VPA	RUF, TPM, VNS	Tonic GTC	5/mo 18/mo	No No	34	Diarrhea	< 50% seizure reduction with addition of CBD (19 mg/kg/d) to RUF, TPM, and VNS

Table 2 (continued)

*New seizure type arising during the study

AA atypical absences, *ACTH* adrenocorticotropic hormone, *ACZ* acetazolamide, *AEDs* antiepileptic drugs, *ALT* alanine transaminase, *AST* aspartate transaminase, *B6* pyridoxine, *CBZ* carbamazepine, *CLB* clobazam, *CLN* clonazepam, *CS* corticosteroids, *DS* Dravet syndrome, *EE* epileptic encephalopathy, *EIMFS* epilepsy of infancy with migrating focal seizures, *EMA* epilepsy with myoclonic absences, *ETZ* ethosuximide, *F* female, *FBM*, felbamate, *FE* focal epilepsy, *FM* focal motor seizure, *GE* generalized epilepsy, *GTC* generalized tonic–clonic seizure, *HTS* hypermotor tonic spasms, *IVIg* intravenous immunoglobulin, *KBr* potassium bromide, *KD* ketogenic diet, *LCM* lacosamide, *LEV* levetiracetam, *LGS* Lennox–Gastaut syndrome, *LTG* lamotrigine, *LZP* lorazepam, *M* male, *MA* myoclonic absences, *MJ* myoclonic jerks, *MTZ* methsuximide, *OXC* oxcarbazepine, *PB* phenobarbital, *PHT* phenytoin, *P5P* pyridoxal-5-phosphate, *RUF* rufinamide, *SE* status epilepticus, *SG* secondarily generalized seizure, *STP* stiripentol, *TA* tonic-atonic seizure, *TPM* topiramate, *VGB* vigabatrin, *VNS* vagal nerve stimulator, *VPA* valproic acid, *ZNS* zonisamide

Table 3 Adverse and serious adverse events reported amongst a cohort of pediatric patients receiving cannabidiol adjunctive therapy

Adverse events, *n* (%)	Study subjects (*n* = 26)
No adverse events	5 (19.2)
Decreased appetite/food aversion	10 (38.4)
Diarrhea/loose stools	9 (34.6)
Weight loss	8 (30.7)
Increased seizures	4 (15.4)
Increased AED concentrations	3 (11.5)
Elevated AST and ALT with concurrent VPA	3 (11.5)
Nausea/vomiting	2 (7.7)
Somnolence/drowsiness	2 (7.7)
Agitation	2 (7.7)
Insomnia	2 (7.7)
Anxiety	1 (3.8)
Fatigue/lethargy	1 (3.8)
Serious adverse events, *n* (%)	6 (23.1)
Hypoalbuminemia	1 (3.8)
Status epilepticus	3 (11.5)
Catatonia/psychosis	2 (7.7)

AED antiepileptic drug, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *VPA* valproic acid

DS, for whom prolonged video-EEG prior to initiation of CBD had shown frequent multifocal and diffuse epileptiform abnormalities, the prolonged video-EEG performed after the emergence of catatonia and during seizure freedom was markedly improved, with no epileptiform abnormalities. Details of AEs for each individual patient are provided in Table 2.

3.3 Efficacy

Responder rates (> 50% seizure reduction) fluctuated during the first 2 years, 38.4% (10/26) at 3 months, 56.7% (15/26) at 6 months, 42.3% (11/26) at 9 months, 38.4% (10/26) at 12 months, 42.3% (11/26) at 18 months, and 34.6% (9/26) at 24 months. Responder rates subsequently declined to 26.9% (7/26) by 36 months and remained stable through the last follow-up (Fig. 2a). In addition to the two patients discontinuing CBD because of AEs, 15 patients (57.7% of the cohort) discontinued therapy for lack of efficacy. The long-term retention rate after 24 months for CBD adjunctive therapy was 34.6% (9/26) (Fig. 2b). Patients continuing treatment included the seven responders, as well as two patients showing < 50% motor seizure reduction, who nevertheless have continued on treatment through to the present.

While all patients reached the CBD dose of 25 mg/kg/day, for some, the dose was subsequently reduced for AEs as described above, and for others the dose was not adjusted

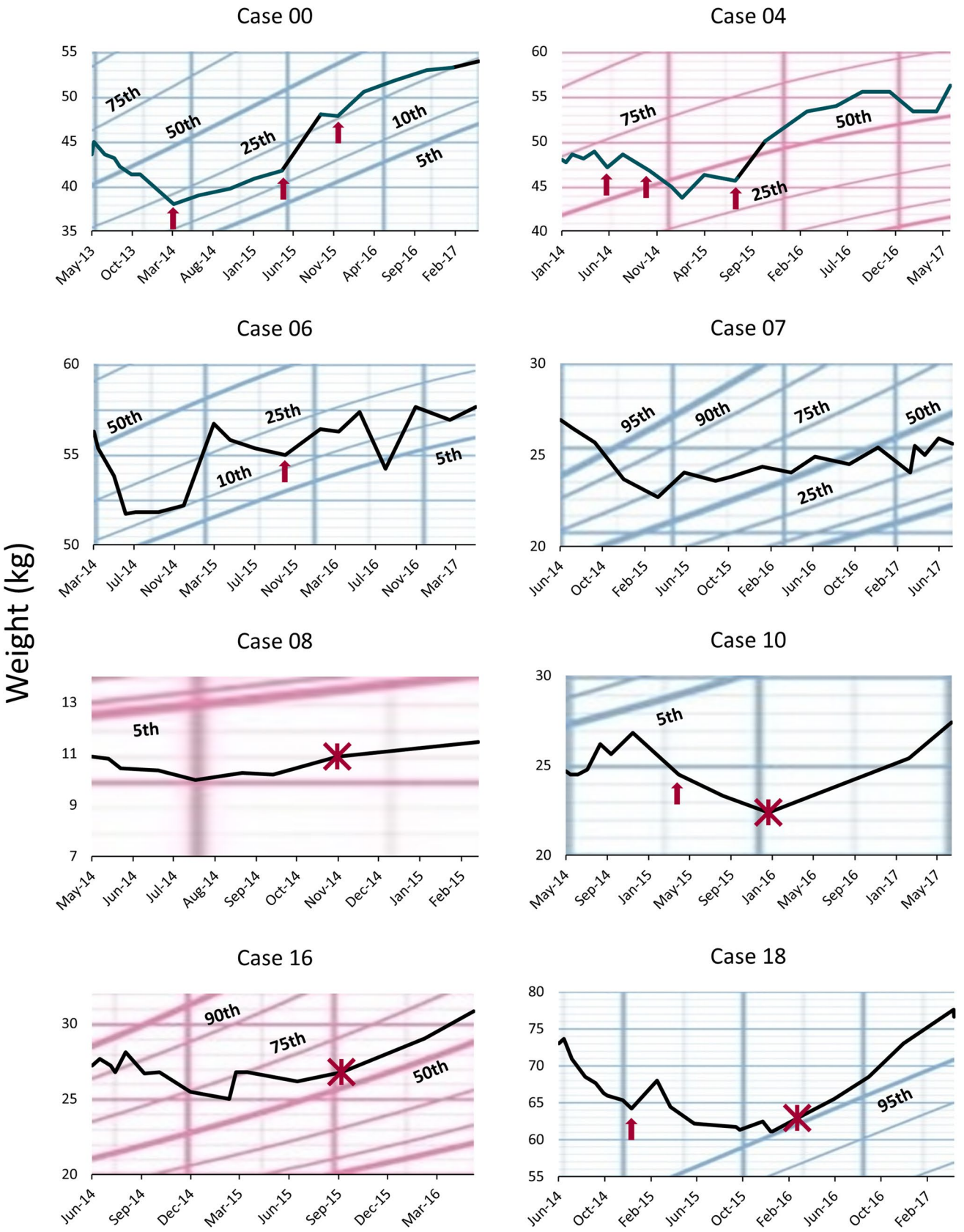

Fig. 1 Weight trajectories in patients with reported clinically significant weight loss over the course of treatment superimposed on growth charts showing weight percentiles for their age. Arrows indicate cannabidiol dose reduction and asterisks indicate when cannabidiol was discontinued

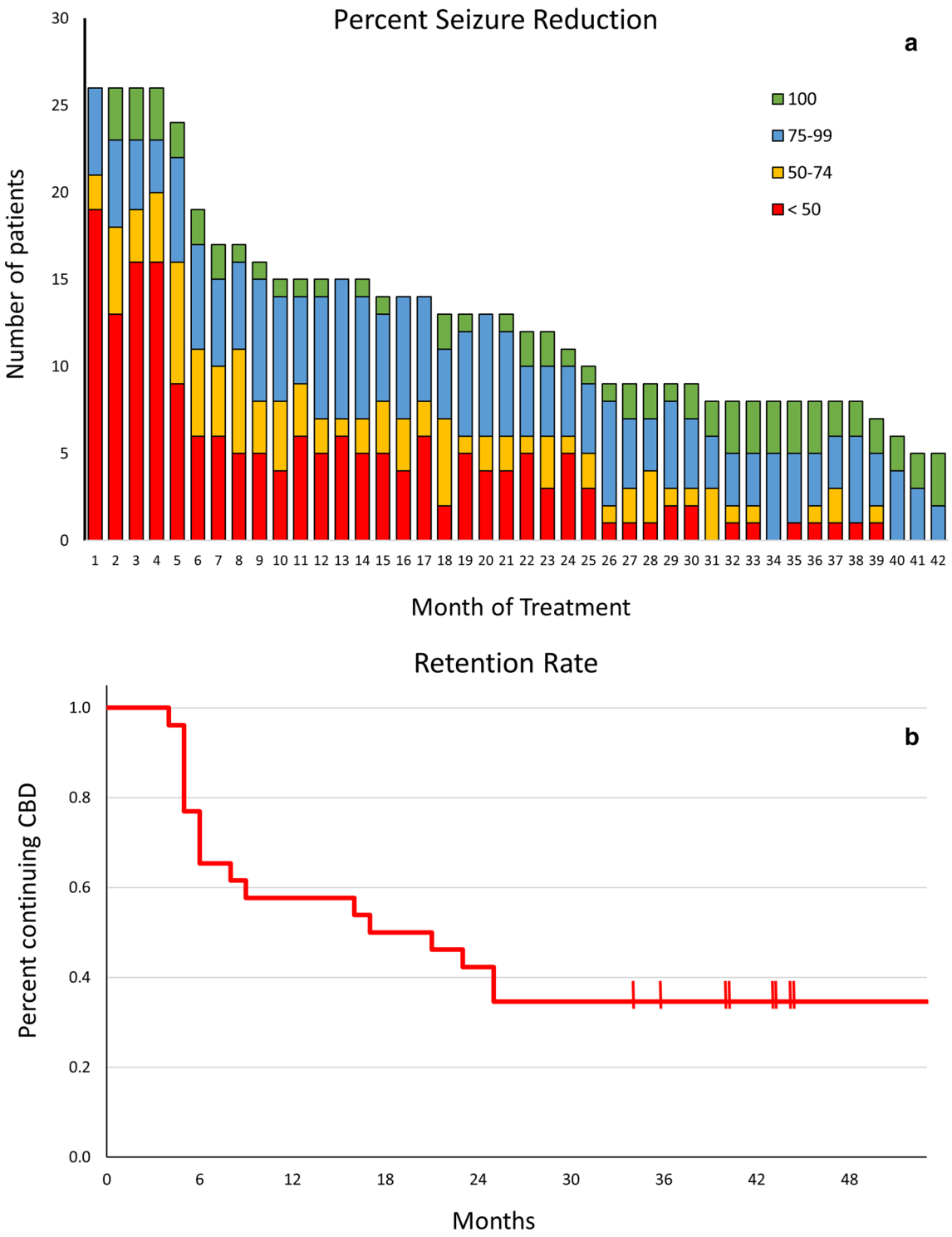

Fig. 2 Efficacy and retention with cannabidiol (CBD) in pediatric epilepsy. **a** Treatment response category by month of therapy in terms of absolute numbers of patients: green indicates seizure free; blue indicates a 75–99% reduction; yellow indicates a 50–74% reduction; red indicates a < 50% reduction. **b** Kaplan–Meier survival curve showing the proportion of subjects continuing CBD therapy. Tick marks = censored

for weight as they grew. Response was associated with doses ranging from 9 to 25 mg/kg/day. Dose adjustments in each patient are noted in Table 2.

Three patients achieved seizure freedom during the study period as follows: at baseline, case 04 had more than 50 generalized tonic–clonic seizures (GTCs) per month and ten emergency department admissions in the 6 months preceding the addition of CBD to her regimen (Table 2 of the ESM). She became seizure free during the initial titration and remained seizure free apart from breakthrough seizures in the setting of missed medication doses or attempts to decrease her AEDs over the next 42 months. Two patients (cases 00 and 06) with EMA and over 75 myoclonic absences daily at baseline had a >75% reduction in these seizures by the third month of adding CBD. Case 00 was weaned off concurrent medications and was taking CBD monotherapy for 19 months with sustained response of the myoclonic absences, but then began having GTCs as a new seizure type, consistent with the course of this epilepsy syndrome. Case 06 had GTCs at baseline that likewise did not respond to the addition of CBD. In each of these patients, the later addition of VPA to their regimen led to lasting freedom from both myoclonic absences and GTCs over the next 2 years. The complete control of myoclonic absences in these patients was confirmed with 24-h video-EEG monitoring. Details of treatment responses for each individual patient are provided in Table 2.

4 Discussion

In our cohort, the addition of CBD was associated with a clinically meaningful reduction in seizure frequency in a proportion of patients with medically refractory epilepsy over a 2- to 4-year period. However, AEs were frequent and often emerged only over time.

4.1 Efficacy

In the natural history of epilepsy, seizures may take a variable course with periods of relative exacerbation and periods of relative improvement. 'Honeymoon' periods of initial response have been described [6] and short-term studies may overestimate treatment efficacy if there is inadequate time to assess a sustained clinically meaningful response [7]. In our cohort, the number of patients with a >50% reduction in motor seizures was between 38 and 57% in the first several months of therapy, in line with the 38–50% response reported in studies of CBD in pediatric epilepsy with follow-up periods in the order of months [2, 3, 8]. In this longer study, the responder rate declined over time, ultimately stabilizing at approximately 26.9% after the first 18 months.

The determinants of treatment response are unclear. Responders in our cohort included two of six patients with DS (33.3%), one with seizure freedom, and the other with a >75% seizure reduction in GTCs. For each of these patients (cases 01 and 04), the rates of emergency department admissions decreased accordingly (Table 2 of the ESM). A recently published randomized controlled trial demonstrating some efficacy of CBD for DS reported a similar percentage of patients with a >75% seizure reduction (14/52, 26.9%) [3]. Responders in our cohort also included two patients with EMA, another patient with generalized epilepsy, and one patient with an acquired focal epilepsy, suggesting that response to CBD therapy may be seen in patients across broad categories of epilepsy, although generalized seizures tended to be more affected by the introduction of CBD compared with focal seizures or epileptic spasms. Best responders tended to be taking concurrent treatment with benzodiazepines (5/7) and/or topiramate (3/7) and VPA (2/7). To what extent this represents a synergistic effect and/or the influence of CBD on the concentrations of other AEDs, especially with regard to CLB, should be explored in future studies. Of particular interest, the two patients with medically refractory EMA became seizure free with a regimen of VPA and CBD.

Retention rate is a combined measure of efficacy and tolerability, as well as patient preference [9]. A majority of the cohort discontinued CBD for lack of efficacy. Previous work has shown that continuation of treatment with artisanal *Cannabis*-based products is associated with the perception of efficacy and has suggested that a higher frequency and severity of seizures (e.g., in DS) could facilitate a more rapid determination of benefit [10]. Our cohort, treated with purified CBD, had a high seizure frequency and most patients without clear benefit discontinued treatment by the 6-month mark with the remainder stopping more gradually between 18 and 24 months. In this way, the retention rate approached the responder rate over time and was 34% by the end of the study period, comparable to the retention rate reported for other AEDs [11], but definitely lower than the 76% retention rate recently reported for CBD [5].

4.2 Adverse Events

As previously published [2–5], AEs were very common, especially decreased appetite, diarrhea (explosive in some cases), and weight loss. While diarrhea could be related to the oil-based drug vehicle, we believe that the lack of appetite and subsequent weight loss are directly related to CBD, as this occurred also independently from the diarrhea. Clinically significant weight loss emerged typically only after about 6 months of treatment and affected almost one-third of the cohort. Weight loss or stagnation in weight

gain led to changes in weight percentiles (Fig. 1, Table 1 of the ESM). This is an important consideration, as even inadequate weight gain can constitute failure to thrive in the pediatric population. Case 10, who was underweight at baseline (below 2 standard deviations of the mean for age), had a − 16.6% additional loss (to below 3 standard deviations) that did not respond to dose reduction. Cannabidiol was discontinued with a subsequent rebound in weight, supporting a direct treatment effect (Fig. 1). A similar response to dose reduction or cessation of treatment could be appreciated in other patients as plotted in Fig. 1. That this has not yet been reported in prior studies could be a result of their shorter duration (14 weeks) [2, 3]. However, a recent report of patients treated with CBD for a median of 48 weeks, while confirming the frequent occurrence of AEs such as diarrhea (29% of patients) and decreased appetite (14% of patients), did not mention weight loss [5].

Serious AEs were seen in six patients of our cohort, including three cases with status epilepticus, two patients with catatonic psychosis, and one patient with hypoalbuminemia. Of the three patients with episodes of status epilepticus during the treatment period, these were consistent with the patients' prior epilepsy courses, except for one patient with DS in whom the increase of seizure frequency paralleled the titration of CBD, leading to discontinuation of treatment (case 02). In two patients, new seizure types were noted during the treatment period: GTC in one patient with EMA (case 00) and atypical absence in a patient with DS (case 01). In each case, the new seizure types were consistent with the natural history of their epilepsy syndrome. Both patients happened to be amongst the responders, suggesting that while CBD was effective in reducing seizures in these patients, it did not alter the course of the epilepsy itself.

Two patients developed catatonia during the observation period. In one patient (case 04) with DS, catatonia developed following a dramatic response to CBD (seizure freedom from a baseline of over 50 seizures per month with ten emergency department visits for frequent seizures in the 6 months preceding therapy initiation). The EEG ruled out non-convulsive status epilepticus and indeed was improved, showing a disappearance of epileptiform abnormalities. A reduction in the CBD dose to 12 mg/kg/day resulted in a reduction in echolalia and increased environmental responsivity. However, attempts to reduce CBD to 10 mg/kg/day led to seizure recurrence. Epilepsy and psychiatric disorders are complex interrelated conditions. Forced normalization describes the emergence of psychotic symptoms in the setting of newly established seizure control [12, 13]. The precise mechanism of this phenomenon is unknown, but it can occur whether convulsions are controlled by medication, surgery, or neurostimulation. We interpret the catatonic psychosis seen in this patient as the result of forced normalization rather than a direct effect of CBD. Indeed, seizures in DS are typically resistant to AEDs and forced normalization manifesting with catatonic psychosis has been previously reported in a patient with DS following seizure control [14].

As reported [15], we noted increased CLB concentrations in three patients taking concurrent therapy. We also noted increased phenobarbital and potassium bromide concentrations in another patient. Cannabidiol is known to inhibit cytochrome P450 2C19, explaining its effects on CLB metabolism. The effect we observed on phenobarbital concentrations may be mediated by the same phenomenon. The mechanism for the increased bromide concentrations is unclear. Consistent with other reports, we also noted the elevation of alanine aminotransferase and aspartate aminotransferase levels with concurrent VPA therapy in two patients [16]. In these patients, the effect resulted from the addition of VPA to regimens that included CBD rather than from the addition of CBD to VPA as reported previously, demonstrating that the sequence of introduction is inconsequential. Our results add to a growing list of drug–drug interactions for CBD in patients with epilepsy [16].

4.3 Strengths and Limitations

Strengths of this study include video-EEG confirmation for every seizure type for every patient, frequent follow-up during a treatment period extending over 3–4 years, allowing for recognition of weight loss/poor weight gain as an emergent AE, and the determination of long-term treatment response and retention rates. Video-EEG confirmation of seizure types is of particular importance, as abnormal non-epileptic movements may account for a substantial number of apparently medically refractory seizures in patients with epilepsy associated with neurodevelopmental disability and this is the population of interest for novel therapeutics.

Our study has limitations. The single-center nature of the study, which facilitated the acquisition of high-quality and detailed patient data (e.g., genotypes, confirmation of seizure types with EEG recordings, emergency department admission data), may also limit external validity. The cohort, while perhaps representative of the heterogeneous pediatric patient population seen in tertiary care centers for medically intractable epilepsy, is too small to allow more than speculative conclusions regarding patients with specific epilepsies. Because most patients discontinued treatment after several months, the number of patients exposed to CBD over a period of years is small and the rate of adverse effects over time may well be underestimated. Bias resulting from the high expectations for cannabis-related treatments has been documented in a study from Colorado in which a reported

response to cannabis extracts was more than twice as likely in new residents, i.e., those who had made the investment of moving to Colorado for cannabis therapy [17]. Our study is subject to this same cannabis anticipation bias, given the open-label design. Finally, while following a pragmatic design in which providers could alter concurrent AEDs may reflect real-world practice, it also confounds the interpretation of our results.

5 Conclusion

Cannabidiol imparted a clinically meaningful reduction in seizure frequency to a subset of patients with medically refractory epilepsy that was sustained over a period of 2–4 years. Responders included patients with DS, patients with EMA, and patients receiving concurrent therapy with VPA, topiramate, and benzodiazepines. However, AEs affected 80.8% of the cohort, including 23.1% with serious AEs. Weight loss, decreased appetite, and diarrhea were frequent and mostly dose dependent. Drug-related status epilepticus, although rare, should be considered.

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Compliance with Ethical Standards

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Conflict of interest Maria Roberta Cilio received support from the Epilepsy Therapy Project from the Epilepsy Foundation and has received research funding, paid to her institution, from Insys Therapeutics for a company-sponsored trial. She has also received fees and travel support for serving on a scientific advisory board from Bio-Marin Pharmaceuticals. Michael S. Oldham is currently affiliated with Medpace, Cincinnati, OH, USA. Tristan T. Sands, Shahryar Rahdari, Michael S. Oldham, Eduardo Caminha Nunes, and Nicole Tilton have no conflicts of interest that are directly relevant to the contents of this article.

Ethics Approval The study was approved by the Human Research Ethics Committee of the UCSF Benioff Children's Hospital.

Consent to Participate Parents provided written informed consent, and patients provided assent according to their physical and mental capability.

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