CNS Drugs (2021) 35:265–281
https://doi.org/10.1007/s40263-021-00807-y

SYSTEMATIC REVIEW

Highly Purified Cannabidiol for Epilepsy Treatment: A Systematic Review of Epileptic Conditions Beyond Dravet Syndrome and Lennox–Gastaut Syndrome

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Accepted: 10 March 2021 / Published online: 22 March 2021
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Abstract

Background Cannabidiol (CBD), which is one major constituent of the *Cannabis sativa* plant, has anti-seizure properties and does not produce euphoric or intrusive side effects. A plant-derived, highly purified CBD formulation with a known and constant composition has been approved by the US Food and Drug Administration for the treatment of seizures associated with Dravet syndrome, Lennox–Gastaut syndrome, and tuberous sclerosis complex. In the European Union, the drug has been authorized by the European Medicines Agency for the treatment of seizures associated with Dravet syndrome and Lennox–Gastaut syndrome, in conjunction with clobazam, and is under regulatory review for the treatment of seizures in patients with tuberous sclerosis complex.

Objectives This systematic review aimed to summarize the currently available body of knowledge about the use of this US Food and Drug Administration/European Medicines Agency-approved oral formulation of pharmaceutical-grade CBD in patients with epileptic conditions, especially developmental and epileptic encephalopathies other than Dravet syndrome and Lennox–Gastaut syndrome.

Methods The relevant studies were identified through MEDLINE and the US National Institutes of Health Clinical Trials Registry in October 2020. There were no date limitations or language restrictions. The following types of studies were included: clinical trials, cohorts, case-control, cross-sectional, clinical series, and case reports. Participants had to meet the following criteria: any sex, any ethnicity, any age, diagnosis of epilepsy, receiving plant-derived, highly purified (> 98% w/w) CBD in a sesame oil-based oral solution for the treatment of seizures. Data extracted from selected records included efficacy, tolerability, and safety outcomes.

Results Five hundred and seventy records were identified by database and trial register searching. Fifty-seven studies were retrieved for detailed assessment, of which 42 were eventually included for the review. The participants of the studies included patients of both pediatric and adult age. Across the trials, purified CBD was administered at dosages up to 50 mg/kg/day. In a randomized double-blind controlled trial in patients with tuberous sclerosis complex, CBD was associated with a significantly greater percent reduction in seizure frequency than placebo over the treatment period. Open-label studies suggested the effectiveness of CBD in the treatment of children and adults presenting with other epilepsy syndromes than those addressed by regulatory trials, including CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes, SYNGAP1 encephalopathy, and epilepsy with myoclonic absences. The most common adverse events observed during treatment with CBD included somnolence, decreased appetite, diarrhea, and increased serum aminotransferases.

Conclusions The currently available data suggest that response to treatment with a highly purified, plant-derived CBD oil-based solution can be seen in patients across a broad range of epilepsy disorders and etiologies. The existing evidence can provide preliminary support for additional research.

Extended author information available on the last page of the article

Key Points

Pharmaceutical-grade cannabidiol (CBD) represents the first in a new class of antiseizure medications

In randomized controlled trials, CBD reduced seizure frequency in patients with Dravet syndrome, Lennox–Gastaut syndrome, and tuberous sclerosis complex

Open-label studies suggest the effectiveness of CBD treatment in patients with other epileptic conditions than those addressed by regulatory trials

The most common adverse events associated with CBD include somnolence, decreased appetite, diarrhea, and increased serum aminotransferases

1 Introduction

Epilepsy is one of the most common chronic disorders of the brain and affects approximately 70 million people worldwide [1, 2]. Most patients with epilepsy can reach sustained remission, while around one third continues to have seizures despite adequate treatment [3–5]. Although many new medications were approved in the last decades, the burden of drug-resistant epilepsy has remained stable over the years [6]. Treatment-resistant epilepsies have a great impact on cognitive and behavioral function and quality of life, and there is an urgent need to search for new therapeutic options [7].

Cannabis has been used to treat epilepsy since antiquity, and the interest in cannabis-based therapies has increased in the last decade. Cannabidiol (CBD), which is one major constituent of the *Cannabis sativa* plant, has anti-seizure properties and does not produce euphoric or intrusive side effects [8]. The lack of regulation and standardization in the medical cannabis industry, however, raises concerns about the composition and consistency of the products that are dispensed [9].

Recently, a plant-derived, highly purified CBD formulation with a known and constant composition has been approved by the US Food and Drug Administration (Epidiolex®) for the treatment of seizures associated with Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) in patients aged ≥ 2 years and for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients 1 year of age and older. In the European Union, the drug (Epidyolex®) has been authorized by the European Medicines Agency for the treatment of seizures associated with DS and LGS, in conjunction with clobazam (CLB), in patients aged ≥ 2 years and is under regulatory review for the treatment of seizures in patients with TSC. This is the first in a new class of antiseizure medications and the only pharmaceutical formulation derived from the cannabis plant that has undergone review through the approval processes and received marketing authorization for these difficult-to-treat epileptic syndromes.

Clinical evidence about CBD treatment in patients with DS and LGS has been already reviewed [10–12]. Here, we summarize the currently available body of knowledge about the use of this Food and Drug Administration/European Medicines Agency-approved oral formulation of pharmaceutical-grade CBD in patients with other epileptic conditions and suggest implications for clinical practice and future research.

2 Methods

The results of this systematic review were reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

The relevant studies were identified through MEDLINE (accessed by PubMed as of October 2020, week 4) and the US National Institutes of Health Clinical Trials Registry (http://www.clinicaltrials.gov). Search strategies are outlined in the Electronic Supplementary Material (ESM). There were no date limitations or language restrictions. The protocol was not registered previously.

The following types of studies were included: clinical trials, cohorts, case-control, cross-sectional, clinical series, and case reports. Self-reported surveys, reviews, meta-analyses, editorials, commentaries, and expert opinions were excluded. Participants had to meet the following criteria: any sex, any ethnicity, any age, diagnosis of epilepsy, receiving plant-derived, highly purified (> 98% w/w) CBD in a sesame oil-based oral solution (Epidiolex/Epidyolex®) for the treatment of seizures. We excluded studies that recruited only patients with LGS or DS, non-epilepsy disorders (e.g., pain, sleep), or patients with non-epileptic seizure types (e.g., non-epileptic myoclonus such as Lance–Adams syndrome). The drug manufacturer was contacted for information about any unpublished or ongoing studies. Reference lists of the selected articles were reviewed to identify additional reports of relevant studies.

Two review authors independently assessed studies for inclusion and extracted the following information from included studies: main study author and age of publication, number and demographics of participants, seizure outcomes (e.g., seizure frequency, 50% responder rate, seizure-free

rate, seizure severity), safety outcomes (e.g., adverse event rate, rates of individual adverse events), and other effectiveness and clinical outcomes (e.g., retention rate, cognitive function, behavior, mood, brain imaging). Any disagreement was resolved by discussion with a third review author.

3 Results

Five hundred and seventy records were identified by database and trial register searching. Fifty-seven studies were retrieved for detailed assessment, of which 42 were eventually included for the review (Fig. 1). The included studies were randomized placebo-controlled trials [13, 43, 47], open-label interventional studies and their subgroup analyses [14, 15, 17, 18, 20–24, 26–30, 32, 34–38, 41, 42, 48–52], retrospective chart reviews [39, 44, 46], clinical series [19, 40, 53], and case reports [16, 25, 31, 33, 45, 54]. The participants of the studies included patients of pediatric age [14–17, 19, 28, 30, 31, 40, 41, 45, 46, 50, 52, 53], adult age [25, 32, 33, 36, 47, 48, 51, 54], and both pediatric and adult age [13, 18, 20–24, 26, 27, 29, 34, 35, 37–39, 42–44, 49]. Details of the characteristics of participants and outcomes of the included studies are provided in the ESM.

Across the trials, purified CBD was administered as adjunctive treatment at dosages up to 50 mg/kg/day. Most studies aimed to assess the efficacy and safety of CBD treatment, and study endpoints included seizure frequency reduction, seizure response rate, seizure freedom, change in seizure severity, treatment discontinuation, and occurrence of adverse events. Eight studies were primarily aimed to describe pharmacokinetic analyses or drug–drug interactions between CBD and antiseizure or non-antiseizure medications [17, 23, 25, 33, 39, 43, 47, 54]. Seven studies included cognitive and/or quality-of-life measures [20–22, 32, 36, 50, 51], and three mainly focused on functional brain imaging assessment [35, 49, 51].

18 studies provided outcome data according to individual epileptic conditions or etiologies, including TSC, CDKL5 deficiency, Aicardi syndrome, Doose syndrome, Dup15q syndrome, epilepsy with myoclonic absences, Sturge–Weber syndrome, SYNGAP1 developmental and epileptic encephalopathy, epilepsy of infancy with migrating focal seizures, SCN8A-related epilepsy with encephalopathy, epileptic spasms, focal cortical dysplasia, cerebral dysgenesis, and lissencephaly; efficacy and tolerability data were also available for patients presenting with febrile infection-related epilepsy syndrome, and status epilepticus (Table 1). Twenty-four studies included patients with uncontrolled or treatment-resistant epilepsy of different etiologies, which were listed or not in the original papers, and outcomes were described for the whole cohorts without details for individual conditions (Table 2).

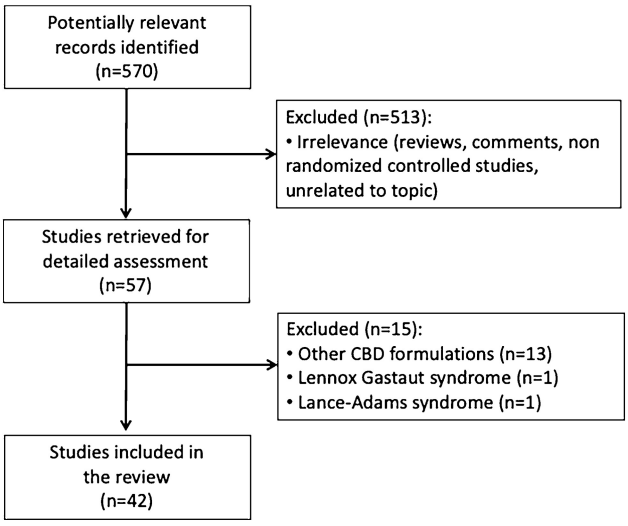

Fig. 1 Flow diagram of the study selection process. *CBD* cannabidiol

4 Discussion

The existing data suggest that response to treatment with a highly purified, plant-derived CBD oil-based solution can be seen in patients across a broad range of epilepsy disorders and etiologies.

The highest-quality evidence is currently available for TSC. In one randomized, double-blind, controlled trial, CBD at both the dosages of 25 and 50 mg/kg/day produced a significantly greater percent reduction in TSC-associated focal and generalized seizure frequency and total seizure frequency, including focal sensory and epileptic spasms than placebo over the treatment period. The 50% responder rate among patients taking CBD was around 40% and substantially overlapped the rate observed in patients with TSC who were recruited in a prior expanded access study of CBD up-titrated to a maximum dose of 50 mg/kg/day within the frame of treatment-resistant epilepsies [20]. Further, the administration of purified CBD as adjunctive therapy at a dosage range of 10–50 mg/kg/day resulted in electrographic and clinical response in patients with TSC with refractory epileptic spasms enrolled in an open-label study: a reduction in epileptic spasm frequency was observed after 2 weeks of treatment, resolution of hypsarrhythmia correlated with the reduction in epileptic spasms, and all patients were free from epileptic spasms at 12 months [41]. Subjective improvements in cognitive and behavioral domains were also seen alongside improvement of background activity [41].

Open-label drug trials provide class III evidence for the efficacy of CBD administration in patients with CDKL5 deficiency disorder and Aicardi, Doose, and Dup15q

Table 1 Main clinical outcomes according to epilepsy condition or etiology

Epilepsy condition/etiology	Population	Main findings
Tuberous sclerosis complex	$N = 224$ (CBD25: $n = 75$, CBD50 $n = 73$, placebo $n = 76$) [13]; $N = 2$, [17] $N = 18$ [20] $N = 25$ [39]; $N = 3$ [41]	*Randomized, double-blind, placebo-controlled trial* Reduction in TSC-associated seizure frequency: 48.6% (CBD25; $p < 0.001$), 47.5% (CBD50; $p = 0.002$), 26.5% (placebo); responder rate TSC-associated seizure frequency: 36.0% (CBD25; $p = 0.069$), 39.7% (CBD50; $p = 0.025$), 22.4% (placebo); reduction in total seizure frequency: 48% (CBD25; $p = 0.001$), 48% (CBD50; $p = 0.002$), 27% (placebo) during 16-week treatment period. Improvement in overall condition on S/CGIC: 69% (CBD25; $p = 0.007$), 62% (CBD50; $p = 0.058$), 40% (placebo) Treatment withdrawal: 10.3%. AEs: 88.0% (CBD25), 97.3% (CBD50), 89.5% (placebo); diarrhea: 30.7% (CBD25), 54.8% (CBD50), 25.0% (placebo); decreased appetite: 20.0% (CBD25), 23.3% (CBD50), 11.8% (placebo); somnolence: 13.3% (CBD25), 26.0% (CBD50), 9.2% (placebo); vomiting: 16.0% (CBD25), 17.8% (CBD50), 9.2% (placebo); pyrexia: 18.7% (CBD25), 16.4% (CBD50), 7.9% (placebo); increased transaminases: 12.0% (CBD25), 24.7% (CBD50), 0% (placebo). SAEs: 21.3% (CBD25), 13.7% (CBD50), 2.6% (placebo) [13] *Open-label studies* Seizure frequency reduction: 58–93% (week 8) [17] Reduction in epileptic spasm frequency: 15.1–98.8% (week 2), 3.7–94.2% (M1), 58.3–100% (M2), 49.1–100% (M3), 80.2–100% (M6), 85.8–100% (M9), 100% (M12) [41] Seizure frequency reduction >50%: 50% (M2), 50% (M3), 38.9% (M6), 50% (M9), and 50% (M12) for all seizure types; 100% (M2), 75% (M3), 100% (M6), 100% (M9), and 100% (M12) for spasms; 75% (M2), 75% (M3), 75% (M6), 75% (M9), and 50% (M12) for atonic seizures; 50% (M2), 66.7% (M3), 50% (M6), 60% (M9), and 100% (M12) for tonic clonic seizures; 38.5% (M2), 53.8% (M3), 30.8% (M6), 53.8% (M9), and 50% (M12) for focal seizures with impairment of consciousness or awareness; 25% (M2), 50% (M3), 50% (M6), 66.7% (M9), and 50% (M12) for focal seizures evolving to bilateral generalized convulsive seizures; 57.1% (M2), 42.9% (M3), 57.1% (M6), 66.7% (M9), and 50% (M12) for tonic seizures [20] Treatment withdrawal: 16.7% [20] Resolution of hypsarrhythmia: 2/2 [41] Cognitive gains 12/14 (85.7%), behavioral improvement 6/9 (66.7%) [20] AEs: 54.2%. Drowsiness 22.9%, diarrhea 14.6%, ataxia 12.5%, agitation 10.4%, irritability 6.3%, lethargy 6.3%, appetite loss 4.2%, poor sleep 4.2%, confusion, vomiting, abdominal pain, mouth sores, increased acne, ankle swelling, sinusitis, mild elevation of transaminases, increased phenytoin level, increased self-stimulation, behavioral difficulties (all 2.1%) [17, 20, 39, 41] CBD daily dose: 15–50 mg/kg [20]; 5–20 mg/kg [39]

Table 1 (continued)

Epilepsy condition/etiology	Population	Main findings
Aicardi syndrome	$N = 19$ [27]	Median decrease in convulsive seizure frequency: 58.3% (week 12), 59.2% (week 48). Responder rate (convulsive seizures): 71% (week 12), 71% (week 48). Mean CBD daily dose: 8.1 ± 2.3 (week 2), 26.7 ± 12.7 (week 12), 32.0 ± 12.3 (week 48) mg/kg
CDKL5 deficiency	$N = 1$ [17]; $N = 20$ [27]; $N = 5$ [30]	Seizure frequency reduction: 100% (week 8) [17] Median decrease in convulsive seizure frequency: 40.8% (week 12), 59.7% (week 48). Responder rate (convulsive seizures): 41% (week 12), 53% (week 48) [27] Responder rate 1/5, increased seizure frequency 2/5 (any seizure types; 8–36 months) [30] Increased seizure frequency: (any seizure types): 2/5 [30] AEs: 4/5. Drowsiness, weight loss, sleepiness, diarrhea, loose stools, agitation. Treatment withdrawal: 4/5 (at 5–23 months) [30] Mean CBD daily dose: 8.3 ± 2.6 (week 2), 18.2 ± 7.0 (week 12), 26.2 ± 10.1 (week 48) mg/kg [27]
Doose syndrome	$N = 2$ [17]; $N = 8$ [27]	Seizure frequency reduction: 54–100% (week 8). AEs: 50% (drowsiness) [17] Median decrease in convulsive seizure frequency: 58.6% (week 12), 28.8% (week 48). Convulsive seizures responder rate: 43% (week 12), 57% (week 48) [27]. Mean CBD daily dose: 8.8 ± 2.5 (week 2), 22.0 ± 5.3 (week 12), 27.5 ± 15.5 (week 48) mg/kg [27]
Dup15q syndrome	$N = 1$ [17]; $N = 8$ [27]	Seizure frequency reduction: 26% (week 8) [17] Median decrease in convulsive seizure frequency: 25.0% (week 12), 38.4% (week 48). Convulsive seizures responder rate: 38% (week 12), 38% (week 48) [27] AEs: 1/1; ataxia, tremor, loss of appetite [17]. Mean CBD daily dose: 8.7 ± 1.9 (week 2), 18.4 ± 7.4 (week 12), 29.2 ± 9.1 (week 48) mg/kg [27]
Epilepsy with myoclonic absences	$N = 5$ [30]	Responder rate 2/5, seizure freedom 2/5, increased seizure frequency: 2/5 (any seizure types; 5–53 months) Treatment withdrawal: 3/5 (at 5–6 months) AEs: 5/5; decreased appetite/food aversion, weight loss, elevated transaminases, loose stools, lethargy
Sturge–Weber syndrome	$N = 5$ [21]	Seizure frequency reduction: 10–90% (week 14), 12–100% (at most recent visit – week 6–60). Treatment withdrawal for lack of efficacy: 2/5 (at week 9 and 38) AEs: 5/5; temporary increased seizures (3/5), behavioral issues (2/5), increased transaminases (1/5), tiredness (1/5) All patients reported improvements in quality of life; subjective improvements in motor, speech, and cognitive abilities, level of alertness, vocalization or communication, mood and behavior also reported. CBD daily dose: 5–25 mg/kg

Table 1 (continued)

Epilepsy condition/etiology	Population	Main findings
SYNGAP1 developmental and epileptic encephalopathy	*N* = 3 [53]	Seizure frequency reduction: 0–85% (M2), 80-95% (M9). Responder rate: 2/3 (M2), 3/3 (M9) AEs: 1/3 (sleep disorder). Slight increase in transaminases (1/3) EEG improvement in background activity and interictal anomalies Caregivers evaluated as much improved the status of their children. Maximum CBD daily dose: 10–23 mg/kg
Epilepsy of infancy with migrating focal seizures	*N* = 1 [16]; *N* = 1 [30]; *N* = 2 [40]	Reduction in seizure frequency >90 at M6, with seizure-free periods; improvement in alertness [16] CBD discontinued after 6 months for inefficacy [30] Overall seizure frequency change −12% to +20% during 24-week treatment period; increase in motor arrest seizures with clinically meaningful reduction in seizure intensity, reduction in generalized clonic seizures, reduction/increase in asymmetric tonic seizures [40] AEs: 75%. Somnolence 2/4, intermittent vomiting 1/4 [16, 30, 41]. Maximum CBD daily dose: 25 mg/kg [16, 40]
SCN8A epileptic encephalopathy	*N* = 1 [30]	CBD dose reduced for side effects and discontinued after 25 months for inefficacy AEs: drowsiness, somnolence
Infantile/epileptic spasms	*N* = 9 [14]; *N* = 9 [15]; *N* = 6 [41]	Day 15: freedom of clinical spasms 0/9; resolution of hypsarrhythmia 0/9; improvement at CGIC 7/9; improvement at PGIC 6/9; AEs 5/9 (55.6%); diarrhea 2/9 (22.2%), upper respiratory tract infection 2/9 (22.2%), somnolence 1/9 (11.1%); serious AEs 1/9 (11.1%) [14] Freedom of clinical spasms: 1/8 (day 29), 2/6 (day 43), 1/4 (day 127), 1/3 (day 211), 1/2 (day 295), 3/7 (day 379). Resolution of hypsarrhythmia: 1/8 (day 29), 0/6 (day 43), 1/4 (day 127), 0/3 (day 211), 1/2 (day 295), 3/7 (day 379). Freedom of clinical spasms and resolution of hypsarrhythmia: 1/8 (day 29), 0/6 (day 43), 0/4 (day 127), 0/3 (day 211), 1/2 (day 295), 3/7 (day 379). Improvement at CGIC: 7/9 (day 29), 6/9 (day 43), 4/9 (day 127), 3/9 (day 211), 3/9 (day 295), 6/9 (day 379); improvement at PGIC: 4/9 (day 29), 5/9 (day 43), 4/9 (day 127), 1/9 (day 211), 1/9 (day 295), 4/8 (day 379). AEs (day 417): 7/9 (77.8%); SAEs (day 417): 2/9 (22.2%) [15] Change in epileptic spasm frequency: −100% to 10.6% (week 2), −96.0% to 10.6% % (M1), −100 to 9.6% (M2), −100 to 12.3% (M3), −100 to −29.8% (M6), −100 to −76.2% (M9), −100 to −42.4% (M12). Resolution of hypsarrhythmia: 3/6. Improvement in cognitive and developmental motor skills: 2/6 [41]. Maximum CBD daily dose: 40 mg/kg [14, 15]
Focal cortical dysplasia	*N* = 2 [49]	Seizure frequency reduction from 70 to 100%, seizure freedom in 1/2 after receiving a stable dosage of CBD for at least 2 weeks. CBD daily dose: 15–20 mg/kg

Table 1 (continued)

Epilepsy condition/etiology	Population	Main findings
Cerebral dysgenesis	$N = 3$ [17]; $N = 1$ [41][a]	Change in seizure frequency: −74% to 99% (week 8); increase in seizure frequency: 2/3 [17] Reduction in epileptic spasm frequency: 100% (week 2), 92.5% (M1), 82.5% (M2), 60% (M3), 67.5% (M6), 85% (M9), 85% (M12) and resolution of hypsarrhythmia [41] AEs: 4/4. Drowsiness (3/4), ataxia and urinary retention (1/4) [17]
Lissencephaly	$N = 1$ [17]	Seizure frequency reduction: 94% (week 8). AEs: none
Tumor-related epilepsy	$N = 3$ [24]; $N = 2$ [49]	Seizure frequency reduction on-study 58–94% (month 2–11) in 2/3 Seizure frequency reduction from 57 to 86% after receiving a stable dosage of CBD for at least 2 weeks [49] Seizure frequency increase in 1/5 [24, 49] Improvement in seizure severity as assessed by CSSS (3/3) and total Mood Disturbance score (2/3) [24]. CBD daily dose: 20–50 mg/kg [24]; 25 mg/kg [49]
Febrile infection-related epilepsy syndrome	$N = 7$ [19]	Resolution of status epilepticus in 1 out of 2 patients treated in the acute phase Mean seizure frequency reduction in 5 patients treated in the chronic phase: 90.9% (week 4) and 65.3% (week 48) for all seizure types, 99.6% (week 4) and 62.3% (week 48) for focal motor seizures, 75% (week 4) and 73% (week 48) for generalized tonic-clonic seizures, 99.6% (week 4) and 62.4% (week 48) for focal seizures with impaired consciousness AEs: dizziness (2/7), decreased appetite and weight loss (1/7), nausea/vomiting (1/7). CBD daily dose: 15–25 mg/kg
Super refractory status epilepticus	$N = 1$ [31] $N = 1$ [45]	Clinical seizure freedom achieved on day 12, clinical and subclinical seizure freedom demonstrated on day 64; sequential discontinuation of phenobarbital, midazolam, perampanel, and dose-reduction of lacosamide [31] Reduction of frequency in clinical seizures (from 10 to 0–3 episodes per hour) and midazolam drip successfully weaned off [45] AEs: fatigue, weight gain [31]. Maximum CBD daily dose: 20 mg/kg [31]; 25 mg/kg [45]
Rett syndrome	$N = 1$ [30]	CBD dose reduced for side effects and discontinued after 6 months for inefficacy. AEs: agitation, insomnia, leg cramping
Refractory generalized epilepsy	$N = 1$ [30]; $N = 2$ [49]	Reduction >50% in seizures frequency: 1/1 (generalized tonic-clonic), 1/1 (tonic seizures) after 43 months of CBD treatment [30] AEs: decreased appetite, weight loss, diarrhea, elevated transaminases [30] Change in seizure frequency: −20.8 to 42.8 % after receiving a stable dosage of CBD for at least 2 weeks [49]. CBD daily dose: 20 mg/kg [49]

Table 1 (continued)

Epilepsy condition/etiology	Population	Main findings
Refractory focal epilepsy	$N = 2$ [30]; $N = 13$ [49]	Focal epilepsy (vasculitis). Seizure frequency reduction >50%: 1/1 at 40 months; AE: none [30] Focal epilepsy (unknown etiology). Seizure frequency reduction >50%: 0/1; treatment withdrawal 1/1 (at 5 months); AE: diarrhea [30] Focal epilepsy (encephalitis; $n = 2$): change in seizure frequency −53.9 to −42.9% after receiving a stable dosage of CBD for at least 2 weeks [49]. CBD daily dose: 25 mg/kg [49] Multifocal epilepsy (unknown etiology; $n = 1$): change in seizure frequency −100% after receiving a stable dosage of CBD for at least 2 weeks [49]. CBD daily dose: 25 mg/kg [49] Temporal lobe epilepsy (unknown etiology; $n = 7$): change in seizure frequency −100% to 50%, responder rate 5/7, seizure freedom 2/7 after receiving a stable dosage of CBD for at least 2 weeks [49]. CBD daily dose: 15–25 mg/kg [49] Frontal lobe epilepsy (unknown etiology; $n = 4$): change in seizure frequency −100% to 14.3%, responder rate 3/4, seizure freedom 1/4 after receiving a stable dosage of CBD for at least 2 weeks [49]. CBD daily dose: 15–25 mg/kg [49]

AE adverse event, *CBD* cannabidiol, *CBD25* cannabidiol 25 mg/kg/day, *CBD50* cannabidiol 50 mg/kg/day, *CSSS* Chalfont Seizure Severity Scale, *EEG* electroencephalogram, *M1* month 1, *M2* month 2, *M3* month 3, *M6* month 6, *M9* month 9, *M12* month 12, *SAE* serious adverse event, *S/CGIC* subject/caregiver global impression of change

[a]Patient with West syndrome history

syndromes, which are common causes of epileptic encephalopathies. Add-on treatment with pure CBD was associated with a significant reduction in baseline monthly seizure frequency at week 12, and no difference in seizure percent change was observed between week 12 and week 48, suggesting sustained efficacy. Long-term response to treatment was further reported over 2–4 years in patients with medically refractory epilepsy, including CDKL5 epileptic encephalopathy and epilepsy with myoclonic absences [30]. Remarkably, patients enrolled in these studies were among the most treatment-resistant patients at each center and had syndromes characterized by a poor outcome, with a high incidence of status epilepticus, use of rescue medication, and sudden unexpected death in epilepsy. They had high baseline seizure frequency and a number of concomitant antiseizure medications, and many had never obtained seizure control despite pharmacological and non-pharmacological interventions, including vagus nervus stimulation, dietary changes, and surgical treatments. In this scenario, the rates of seizure response and even seizure freedom for a few cases are suggestive of clinically relevant CBD efficacy.

A significant decrease in seizure frequency from 80 to 95% has been observed with CBD add-on therapy in patients with SYNGAP1 developmental and epileptic encephalopathy, accompanied by an improvement of background electroencephalogram activity and interictal anomalies. The reduction in drop attacks and myoclonic seizures, which are associated with a high risk of seizure-related injuries [55], could determine a favorable effect on the general condition of the patients. Interestingly, syngap1 heterozygous mutations induce an increase in the transient receptor potential cation channel subfamily V member 1 protein, which can be one of the mechanisms underlying the excitatory/inhibitory imbalance in drug-resistant epilepsy related to SYNGAP1 mutations [56, 57], and CBD has been shown to induce a rapid activation and desensitization of the transient receptor potential cation channel subfamily V member 1 [58].

One randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of CBD titrated to a target dose of 40 mg/kg/day in patients with infantile spasms aged 1–24 months had its primary endpoint measure based on an electroencephalogram and was stopped as it met the prespecified "No-Go Criteria" in its pilot phase after the recruitment of nine participants; improvement in caregiver and physician global impression of change was observed in most cases [14]. Clinical improvement following add-on CBD treatment was, instead, clearly observed in children aged between 3 and 16 years who presented with refractory epileptic spasms and participated in one open-label study: around 70% of patients were responders at 2 weeks, one third were free from epileptic spasms after 2 months, and 60% had a resolution in their hypsarrhythmia pattern [41].

Table 2 Main clinical outcomes in patients with treatment-resistant epilepsy

Study, year	Population	Efficacy	Tolerability/safety	Other
Geffrey et al. (2015) [17]	$N = 13$	Mean change in seizure frequency (week 8): 51%; >50% decrease in seizure frequency (week 8): 69.2% Increased seizure frequency: 15.4%	AEs: 76.9%. Drowsiness 46.2%, ataxia 15.4%, irritability 15.4%, restless sleep 7.7%, urinary retention 7.7%, tremor 7.7%, loss of appetite 7.7% Treatment withdrawal: 0%	
Devinsky et al. (2016) [18]	$N = 214$	Median reduction in seizure frequency (week 12): 34.6% (all), 55.0% (focal), 54.3% (atonic), 36.5% (tonic), 16% (tonic-clonic); 36.5% (motor) Seizure freedom (week 12): 4% (motor seizures), 2% (all seizures) Responder rates (week 12): 37% (all seizures), 39% (motor seizures)	AEs: 79.0%. AEs reported in >5% of patients: somnolence 25.3%, decreased appetite 19.1%, diarrhea 19.1%, fatigue 13.0%, convulsion 11.1%, increased appetite 8.6%, SE 8.0%, lethargy 7.4%, weight increased 7.4%, weight decreased 6.2%, drug concentration increased 5.6%; elevated liver functions tests 6.8%. SAEs: 12.3% Drug withdrawal because of AEs: 3.1%	Diarrhea or related side effects (e.g., weight loss) more likely if CBD daily dose >15 mg/kg Somnolence more common in patients taking CLB
Rosenberg et al. (2017) [22]	$N = 48$	Median reduction in seizure frequency (week 12): 39.4% Responder rate (week 12): 41.7%	Somnolence, drowsiness, or fatigue: 58.3%	Improvement in patient QOLCE as assessed by caregivers (energy/fatigue, memory, other cognitive functions, control/helplessness, social interactions, behavior and global QOL item sub-scores), not related to changes in seizure frequency or AEs
Gaston et al. (2017) [23]	$N = 81$		Sedation more frequent with higher N-CLB concentrations in adults and transaminase levels significantly higher in participants taking concomitant VPA Sedation resulted in CLB dose decrease, but not discontinuation	Increases in TPM, RUF, and N-CLB and decrease in CLB serum concentrations with increasing CBD dose. Increases in serum concentrations of ZNS and ESL with increasing CBD dose in adults. Except for CLB and N-CLB, all mean concentration changes were within the therapeutic ranges
Szaflarski et al. (2018) [26]	$N = 607$	Median reduction in seizure frequency (week 12-96): 46–53% (total), 44–51% (convulsive). Responder rate (week 12–96): 48–52% (total), 44–52% (convulsive seizures). Seizure freedom rate (week 12–96): 6–8% (total seizures), 9–13% (convulsive). Seizure frequency increase (week 12–96): 19–25% (total), 20–27% (convulsive). Drug withdrawal for lack of efficacy: 14.7%	AEs: 88.3%; diarrhea 29.2%, somnolence 22.4%, convulsion 16.8%, decreased appetite 12.4%, upper respiratory tract infection 12.4%, vomiting 11.4%, fatigue 10.7%, pyrexia (10.4%), SE 7.4%, pneumonia 6.8%. Increased transaminases: 10% (of which 75% were on VPA). Somnolence more common in patients taking (38%) than not taking (14%) CLB SAEs: 32.8% Drug withdrawal because of AEs: 5.3%	
Chen et al. (2018) [28]	$N = 40$	Seizure frequency not reliably recorded because of disease severity	AEs: 62.5%; somnolence 32.5%, diarrhea 10.0%, anorexia 10.0%, increased seizures 5.0%, vomiting 2.5%, rash 2.5%; increased transaminases 5.0% (all receiving VPA) SAEs: 20.0% Drug withdrawal because of AEs: 5.0%	Improvement at CGIC: 12/40 (30.0%) Improvement at PGIC: 12/40 (30.0%)

Table 2 (continued)

Study, year	Population	Efficacy	Tolerability/safety	Other
Szaflarski et al. (2018) [29]	$N = 132$	Seizure frequency reduction: 63.6% (week 12), sustained with no significant differences at week 24 and week 48 Responder rate: 55.4% (week 12), 51.2% (week 24), 63.9% (week 48) Seizure freedom: 6.2% (week 12), 6.8% (week 24), 3.3% (week 48)	Significant decrease in AEP at week 12 with stable scores thereafter (week 24 and 48) Retention rate: 77% (week 48)	Significant decrease in CSSS scores at 12 weeks and stable thereafter (week 24 and 48)
Gaston et al. (2019) [32]	$N = 53$	Seizure count: at enrollment 41.5% (<14 seizures), 30.2% (14–50 seizures), 28.3% (>50 seizures); at 12 months: 62.3% (<14 seizures), 24.5% (14–50 seizures), 13.2% (>50 seizures)	Improvement in AEP scores at 12 months	Significant decrease in CSSS at 12 months Improvement in POMS and QOLIE-89 total scores at 12 months
Szaflarski et al. (2019) [34]		Median seizure frequency reduction: 54% (at the time of CBD plasma level testing after stable dosage for at least 14 days) Responder rate: 57% (at the time of CBD plasma level testing after stable dosage for at least 14 days)	Diarrhea 30%, sedation 14%, depression and mood issues 7%, nausea/vomiting 3%	Positive linear correlation between CBD dosage and plasma peak concentration Increased CBD concentrations associated with improvement in seizure frequency after adjusting for age
Allendorfer et al. (2019) [35]	$N = 22$	Median seizure frequency: 71.2% after a median time of 10 weeks and achieving a stable CBD dose for at least 2 weeks		Improvements in seizure severity and mood. CBD reduced right superior frontal gyrus and right insula/ middle frontal gyrus activation related to stimulus conflict resolution and reduced differences in condition-based functional connectivity of the right superior frontal gyrus
Martin et al. (2019) [36]	$N = 27$			Improvement in seizure severity at 12 months. No statistically significant score changes in cognitive tests. No statistically significant association between changes in cognitive test performance and CBD dose or seizure severity change
Gaston et al. (2019) [37]	$N = 132$	Sustained reduction in seizure frequency at 12, 24, and 48 weeks		Improvement in seizure severity as assessed by the CSSS at 12, 24, and 48 weeks No significant differences in seizure frequency and severity reduction between CLB-On and CLB-Off patients and between patients taking and not taking interacting ASMs (rufinamide, eslicarbazepine, zonisamide, topiramate)

Table 2 (continued)

Study, year	Population	Efficacy	Tolerability/safety	Other
Savage et al. (2020) [38]	$N = 47$	Seizure frequency reduction: 26.8% (CLB-On), 26.2% (CLB-Off) at M2; 58.5% (CLB-On), 49.5% (CLB-Off) at the best point of seizure control within the first year Responder rate: 50.0% (CLB-On), 26.7% (CLB-Off) at M2; 71.9% (CLB-On), 33.3% (CLB-Off) at the best point of seizure control within the first year Seizure freedom: 3.1% (CLB-On), 0% (CLB-Off) at M2; 6.3% (CLB-On), 0% (CLB-Off) at the best point of seizure control within the first year	Most common AEs: diarrhea, somnolence, fatigue; increased serum aminotransferases in patients taking concomitant VPA. Somnolence, ataxia, irritability, and urinary retention were common in the setting of concomitant CLB use and typically resolved after dose adjustments to either CLB or CBD	No significant difference in mean seizure frequency reduction between patients taking and not taking concomitant CLB. There was a significantly greater responder rate for subjects taking CBD and CLB at the point of best seizure control within the first year of treatment No significant difference in mean CBD doses and no correlation between change in N-CLB or CLB levels and change in seizure frequency
Sharma et al. (2019) [42]	$N = 18$	Reduction in seizure frequency at ≥10 weeks	Reduction in AEP at ≥10 weeks	Voxel-level paired samples t-tests did not identify significant changes in gray matter volume or cortical thickness
Ben-Menachem et al. (2020) 89.1 [43]	$N = 35$; CBD $n = 28$, placebo $n = 6$		**STP arm**: AEs: 66.7% (CBD), 0% (placebo), diarrhea 41.7% (CBD), 0% (placebo), fatigue 25.0% (CBD), 0% (placebo), nausea 16.7% (CBD), 0% (placebo), decreased appetite 16.7% (CBD), 0% (placebo), increased transaminases 16.7% (CBD), 0% (placebo) SAEs: 8.3% (CBD), 0% (placebo) **VPA arm**: AEs: 87.5% (CBD), 25.0% (placebo), diarrhea 68.8% (CBD), 0% (placebo), nausea 12.5% (CBD), 0% (placebo), nasopharyngitis 12.5% (CBD), 0% (placebo). SAEs: 6.3% (CBD), 0% (placebo)	Coadministration of steady-state CBD led to a small increase in exposure to steady-state STP and little effect on VPA exposure
McNamara et al. (2020) [46]	$N = 87$	Seizure frequency improvement in 50.7% of patients	AEs: sedation 26%, behavior change 15%, thrombocytopenia 10%, agitation 6%	All patients with thrombocytopenia were taking VPA. Thrombocytopenia was reversible
VanLandingham et al. (2020) [47]	$N = 20$; CBD = 16, placebo = 4	Seizure frequency improved in 56.3% of patients in CBD group and 25.0% of patients in placebo group (10-day titration period followed by 21-day maintenance period)	AEs: 81.3% (CBD), 50.0% (placebo). Diarrhea 37.5% (CBD), 25.0% (placebo), nausea 18.8% (CBD), 0% (placebo), vomiting 18.8% (CBD), 0% (placebo), dizziness 12.5% (CBD), 0% (placebo), sedation 12.5% (CBD), 0% (placebo), somnolence 12.5% (CBD), 0% (placebo), dermatitis 12.5% (CBD), 0% (placebo) Increased transaminases: 12.5% CBD SAEs: 6.3% (CBD), 0% (placebo) Treatment withdrawal due to AEs: 12.5% (CBD), 0% (placebo)	No evidence of drug–drug interaction between CBD and CLB; significant drug–drug interaction between CBD and N-CLB

Table 2 (continued)

Study, year	Population	Efficacy	Tolerability/safety	Other
NCT02564952 [48]	$N = 18$		AEs: 94.4%. Diarrhea 44.4%, somnolence 38.9%, dizziness 22.2%, headache 22.2%, vomiting 16.7%, fatigue 11.1%, irritability 11.1%, respiratory tract infection 11.1%, seizure 11.1%, hyponatremia 11.1% SAEs: 11.1%	
Thompson et al. (2020) [50]	$N = 38$			Improvement in seizure severity at 12 months as assessed by CSSS No significant change in cognitive performance or functional adaptive status at 1 year
Gaston et al. (2020) [51]	$N = 20$	Change in seizure frequency −100% to +50%, responder rate 70%, seizure freedom rate 30% after reaching a stable dosage of CBD for more than 2 weeks		No significant changes in modified Sternberg working memory task performance; increased activation in inferior frontal gyrus regions in memory encoding
D'Onofrio et al. (2020) [52]	$N = 125$	Seizure frequency reduction: 28.6% (M1), 37.4% (M2), 41.0% (all patients, M6), 42.7% (CLB-On, M6), 38.5% (CLB-Off, M6) Seizure responder (M6): 37.8% (all patients), 43.2% (CLB-On patients), 31% (CLB-Off patients)	AEs: 48.8%. Somnolence 20.8%, fatigue 16.0%, behavioral disorders 12.8%, decreased appetite 9.6%, sleep disturbance 5.6%, diarrhea 4.8%, convulsion 0.8%. Increased transaminases: 9.6% (all patients receiving both CLB and VPA and CLB)	AE and efficacy did not differ between CLB-On and CLB-Off patients Improvement at CGIC. No statistical difference in C/PCGI scores between CLB-On and CLB-Off patients
Cortopassi et al. (2020) [54]	$N = 1$	Seizure frequency reduction 50% (M6)		Increase in INR during CBD titration, which required a nearly 20% warfarin dose reduction

Additional details about population and outcomes of studies are provided in the ESM

AE adverse event, *AEP* adverse event profile, *ASM* antiseizure medications, *CBD* cannabidiol, *CGIC* Caregiver Clinical Global Impression of Change, *CLB* clobazam, *CSSS* Chalfont Seizure Severity Scale, *ESL* eslicarbazepine, *INR* international normalized ratio, *M1* month 1, *M2* month 2, *M6* month 6, *N-CLB* N-desmethylclobazam, *PGIC* Physician Global Impression of Change, *POMS* Profile of Moods States, *QOLCE* Quality of Life in Childhood Epilepsy, *QOLIE-89* Quality of Life in Epilepsy-89, *RUF* rufinamide, *SAE* serious adverse events, *SE* status epilepticus, *STP* stiripentol, *TPM* topiramate, *VPA* valproic acid, *ZNS* zonisamide

In the population of patients with medically refractory epilepsy, CBD given as an adjunct treatment at 5–50 mg/kg/day exhibited an appreciable reduction in seizure frequency in a subset of patients with Sturge–Weber syndrome, focal cortical dysplasia, lissencephaly, brain tumor-related epilepsy, and frontal and temporal lobe epilepsy of unknown etiology. Finally, in the setting of emergency and urgency, pharmaceutical-grade purified CBD proved beneficial in a series of children treated for highly refractory seizures attributed to febrile infection-related epilepsy syndrome and individual cases of refractory status epilepticus.

The overall tolerability profile of purified CBD was favorable across the different epileptic conditions and substantially overlapped that reported in patients with DS and LGS enrolled in randomized controlled trials [10, 11]. The most common adverse events observed during treatment included somnolence, gastrointestinal symptoms, decreased appetite, and weight loss.

The incidence of somnolence was generally higher in patients concomitantly taking CLB. The increased serum level of *N*-desmethyl-clobazam, the active metabolite of CLB, via inhibition of cytochrome P450 2C19 by CBD is likely to contribute to the risk [59]. Slow titration of CBD and dose adjustment of CLB can alleviate the side effect when the two drugs are concomitantly administered [52]. Further, as it is not easy to distinguish benzodiazepine toxicity from CBD-related adverse events on a clinical basis, therapeutic drug monitoring may be recommended before CBD administration and after any dose increase [60].

Gastrointestinal symptoms were generally mild to moderate in severity and usually evident within the first months of treatment. The sesame oil-based drug vehicle and the effects of CBD on the gut microbiome may contribute to diarrhea [61]. The lack of appetite and decreased weight are thought to be directly related to CBD as they occurred also independently from diarrhea [30]. Clinically significant weight loss emerged typically only after about 6 months of treatment.

The currently available data indicate no adverse effects involving cognitive or adaptive functioning related to treatment with purified CBD [36, 50]. Improvement in cognition, behavior, mood, and multiple domains of health-related quality of life has been reported during CBD treatment in patients with TSC [20], children and young adults with severe childhood-onset epilepsy [22], and adult patients with refractory epilepsy [32]. These effects were independent of the reduction in seizure burden and may result from the changes induced by CBD in the connectivity related to executive functioning and emotional and attentional control processes, as observed in functional imaging studies [35, 49, 51]. Further, the lack of any impact on brain morphometry in terms of gray matter volume and cortical thickness changes despite positive action at molecular targets supports the safety of CBD in patients with treatment-resistant epilepsy, at least in the short and intermediate term [42].

Elevation of liver function tests occurred during CBD treatment. Most of the patients who experienced a rise in serum transaminases were concomitantly taking valproic acid (VPA). As CBD does not affect systemic concentrations of VPA or its metabolite, 4-ene-VPA [43], the interaction between CBD and VPA is most likely pharmacodynamic rather than pharmacokinetic. The interaction observed at the level of in vitro hepatic mitochondria could be the mechanism at the basis of the clinical findings [62, 63]. Interestingly, several patients who presented with elevations of liver function tests during the expanded access program were retitrated to baseline CBD dose after the withdrawal of VPA and did not experience any further laboratory abnormalities [23, 26]. Given the risk of hepatocellular injury, slow uptitration and close monitoring of liver enzymes are recommended, mostly during the initial phases of treatment, in patients taking VPA, following changes in the CBD dose and the addition of or changes in medications with known effect on the liver, such as VPA and CLB [64].

A drug–drug interaction that can have clinical relevance is that between CBD and the mechanistic target of rapamycin inhibitors, which are used as treatment options for TSC-associated manifestations, including subependymal giant cell astrocytomas, renal angiomyolipomas, and focal seizures. Cannabidiol can result in increased serum concentrations of sirolimus (or rapamycin) and everolimus, likely via inhibition of cytochrome P450 3A4 [39]. Close monitoring of mechanistic target of rapamycin inhibitor serum concentrations, safety laboratory studies, and occurrence of adverse events is warranted, and a dose reduction may be required. The increase in mechanistic target of rapamycin inhibitor levels can be particularly significant in patients concomitantly treated with the ketogenic diet, as both treatments are associated with similar metabolic derangements [65].

While there was no treatment-related thrombocytopenia during the phase III trials, a single-center systematic chart review reported this adverse event in 10% of the pediatric (aged < 21 years) patients diagnosed with LGS, DS, or other treatment-resistant epilepsies who were prescribed pharmaceutical-grade CBD [46]. Although all patients were concurrently treated with CBD and VPA, thrombocytopenia occurred independently of VPA doses and concentrations, and it was usually reversible with adjustments in the dosage of CBD or VPA; one case recovered spontaneously. If this finding is confirmed, monitoring for thrombocytopenia when adding CBD to a regimen that includes VPA may be also warranted.

The characteristics of the studies comprised in this review need to be considered in the interpretation of the findings. Major limitations included the open-label and uncontrolled

design of the majority of the studies. The lack of blinding and comparator groups increases the potential for bias owing to the variable natural history of seizures and the high expectations for treatment [66]. The issue of the placebo response can be especially relevant in paediatric studies of CBD treatment because of the intense media and family interest in the compound [67]. The expectation of efficacy effect, however, is rarely sustained over time, and studies reporting long-term follow-up data can reduce or control it. Parent-reported measures of quality of life and cognitive and behavioral changes may be subjective views of the caregiver rather than patient experiences, and additional studies are needed to assess the quality of life of caregivers alone or patients themselves [67]. Further, the limited study sizes limited the generalizability of the results and the determination of statistical significance.

5 Conclusions

The approval of CBD represents a milestone in the history of medical use of cannabinoids to treat seizure disorders. Pharmaceutical-grade CBD oral solution is the first product made directly from the cannabis plant rather than created synthetically to be authorized by regulatory agencies, and the first in a new class of antiseizure medications. Experimental data demonstrated that CBD may have antiseizure properties in a broad range of epilepsy syndromes and etiologies [68, 69], and open-label studies suggested the effectiveness of purified CBD in the treatment of children and adults presenting with other epilepsy syndromes and seizure types than those addressed by regulatory trials, including CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes, *SYNGAP1* encephalopathy, and Sturge–Weber syndrome. Of note, results cannot be directly transferred to other cannabis-derived products and non-purified forms of medical marijuana or its components.

Epileptic encephalopathies are associated with treatment-resistant seizures, high medication burden, neurodevelopmental delays, and disabling comorbidities [70]. To date, there are no drugs specifically approved for these conditions, and existing therapies can determine or exacerbate cognitive, behavioral, and motor disorders [27]. The currently available evidence about pharmaceutical-grade CBD provides preliminary support for additional research. It is, however, worth noticing that clinical studies in orphan diseases necessarily vary from trials in non-rare conditions and are less likely to use randomization, blinding, and active comparators [71]. Considering the high morbidity and mortality associated with uncontrolled epilepsy and the challenge to generate significant statistical power within the framework of traditional randomized, controlled trials, novel trial designs should be considered [72].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40263-021-00807-y.

Declarations

Funding No funding was received for the conduct of this study. Open access funding was provided by Università Politecnica delle Marche within the CRUI-CARE Agreement.

Conflict of Interest Simona Lattanzi has received speaker's or consultancy fees from Eisai, UCB Pharma, and GW Pharmaceuticals and has served on advisory boards for Angelini Pharma, Arvelle Therapeutics, BIAL, and GW Pharmaceuticals. Eugen Trinka has received speaker's honoraria from UCB Pharma, Biogen, Gerot-Lannach, Bial, Eisai, Takeda, Newbridge, Sunovion Pharmaceuticals Inc., LivaNova, and Novartis; consultancy funds from UCB Pharma, Biogen, Gerot-Lannach, Bial, Eisai, Takeda, Newbridge, GW Pharmaceuticals, Sunovion Pharmaceuticals Inc., and Novartis; and directorship funds from Neuroconsult GmbH. Eugen Trinka's institution received grants from Biogen, Red Bull, Merck, UCB Pharma, European Union, FWF Österreichischer Fond zur Wissenschaftsförderung, and Bundesministerium für Wissenschaft und Forschung. Pasquale Striano received fees and research grants from GW Pharmaceuticals, Zogenyx, Biomarin, and Kolfarma s.r.l. Chiara Rocchi, Sergio Salvemini, and Mauro Silvestrini have no conflicts of interest that are directly relevant to the content of this study. Francesco Brigo acted as a consultant for Eisai.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material Not applicable.

Author Contributions SL drafted the concept for the article, analyzed the data, and wrote the manuscript. SL, CR, and SS performed the literature search. ET, PS, MS, and FB critically revised the work. All authors contributed to the final manuscript.

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