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REVIEW ARTICLE

Cannabidiol in the Treatment of Epilepsy

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Abstract
Anecdotal reports addressing the successful seizure treatment of severe epilepsies with cannabidiol (CBD) have increased both public interest and academic research. Placebo-controlled, randomized, controlled trials proved the efficacy of pharmaceutical-grade CBD in epilepsy treatment, thus leading to pharmaceutical-grade CBD approval by the US Food and Drug Administration and the European Medicines Agency for the treatment of seizures in Dravet syndrome and Lennox–Gastaut syndrome as well as for tuberous complex syndrome by the Food and Drug Administration only. However, the CBD market is confusing because an array of products of different origins, purity, and concentration is available. Additionally, the results from the pivotal studies with plant-derived, pharmaceutical-grade CBD cannot simply be transferred to other epilepsy types or CBD of any origin. Because of the high demands and expectations that patients with epilepsy and their caregivers have regarding CBD, information outlining the proven facts and potential risks is essential. The aim of this article is to thoroughly review available research data and practical recommendations to provide the treating physician with the necessary information for counseling patients with epilepsy.

Key Points

Cannabidiol is an increasingly demanded, quite expensive treatment option for drug-resistant epilepsy.

Efficacy was shown for selected epileptic encephalopathies such as Dravet syndrome and Lennox–Gastaut syndrome as well as tuberous sclerosis complex; other forms of epilepsy are currently investigated.

There is growing evidence of a positive influence of cannabidiol on behavior and cognition.

1 Introduction

Epilepsy is clinically defined as a syndrome of recurrent unprovoked seizures, or as one seizure with evidence of an increased risk of seizure recurrence of > 60% over the next 10 years [1]. With a prevalence of 0.5–1%, epilepsy is one of the most common neurological diseases. Up to 30% of patients with epilepsy do not achieve seizure freedom with two appropriately chosen antiseizure drugs, hence, have to be considered as drug resistant. Unfortunately, recently developed new-generation antiseizure drugs have not resulted in a significantly higher rate of seizure-free patients, even though the tolerability and interaction profile of newer antiseizure drugs is, generally, more favorable [2, 3]. Seizures, as well as the side effects from antiseizure drugs, co-morbidities, and social consequences of seizures lead to a significant loss in the quality of life for those affected. Therefore, the search for new therapies is still a major challenge for patients and physicians.

Cannabidiol (CBD) is one of the major components of the *Cannabis sativa* plant. This phytocannabinoid was isolated in the 1940s and thoroughly studied thereafter [4]. Cannabidiol is not only used as a food supplement or for general well-being purposes, in fact, it is under investigation for a board variety of disorders, for example, mood disorders, anxiety, pain, or epilepsy [4, 5]. Cannabidiol can be synthesized (synthetic CBD) as well as extracted from *C. sativa* (plant derived). For different formulas [with different tetrahydrocannabidiol (THC) co-content], CBD-rich cannabis to purified CBD, to highly purified pharmaceutical-grade CBD (with THC content lower than 0.2%) are available.

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2 First Cannabidiol Treatment in Epilepsy

Since the last century, the anticonvulsant effects of cannabis have been anecdotally described in small studies of patients with refractory epilepsies [6]. However, the effect of medical cannabis on seizures and epilepsies is, in general, inconsistent. The scientific work-up of the phytocannabinoid CBD has shown promising anticonvulsant effects in different animal models [7, 8]. The mechanism of action of CBD is still not fully understood. However, modulation of intracellular $Ca2^+$ mobilization (by GPR55 and TRPV1) as well as modulation of adenosine-mediated signal pathways seem to play an essential role [9].

Over the past few years, the interest in using CBD for general well-being as well as a treatment option for different diseases has risen. This deluge of personal experiences and reports has inspired patients with epilepsy and their families to try CBD for seizure control. A famous report detailed the treatment course of a 5-year-old girl with Dravet syndrome (DS) who experienced up to 50 bilateral tonic-clonic seizures per month. She experienced a > 90% reduction in seizures with CBD-rich cannabis treatment. This attracted immense attention and raised the interest in treating patients with epilepsy with CBD [10]. Because of a massive amount of media reporting and the expectations and wishes of severely affected patients with epilepsy, the demand for medical cannabis and CBD treatment increased dramatically [11]. In the USA, because of the legal restrictions of cannabis and its compounds, some families even moved to other states with easier access to medical cannabis and CBD to receive this treatment for their children with epilepsy [12].

Prompted by this, studies on CBD in epilepsy were set up. The first prospective data were collected in an observational interventional trial that included 214 children and adolescents with drug-resistant epilepsy of different etiologies. All of them experienced frequent seizures (median about 60 seizures monthly), thus representing a strongly affected group. Cannabidiol was tapered up until intolerance or a maximum of 25 mg/kg/day was achieved. The mean CBD dose was 22.9 mg/kg (safety group) and 22.7 mg/kg (efficacy group), respectively. The median monthly seizure change was − 34.6% for all seizures, − 55% for focal seizures, and − 54.3% for atonic seizures. In contrast, the efficacy for tonic-clonic seizures was worse (− 16%). Responder rates, defined as a reduction of at least 50% of the seizures, were 37% in all seizures, 56% in atonic seizures, 40% in tonic seizures, and 34% in tonic-clonic seizures, thus supporting the idea of CBD having different efficacies in different seizure types. The median reduction and responder rates for motor seizures were higher in the DS patient subgroup (49.8%). In the safety group, 79% of the patients reported adverse events (AEs), and 12% reported drug-related serious AEs. Adverse events led to discontinuation in 3% of the patients. The most common AEs were somnolence (25%), decreased appetite (19%), diarrhea (19%), and fatigue (13%). Six patients experienced thrombocytopenia and 11 had elevated liver enzymes; all of those were taking valproate. This study suggests a reduction in seizure frequency with CBD and an adequate safety profile [13].

3 Pivotal Studies

Four randomized, controlled, double-blind studies were carried out in childhood-onset epilepsies: two in Lennox–Gastaut syndrome (LGS) and two in patients with DS. All of them used plant-derived, pharmaceutical-grade CBD from the same company.

Dravet syndrome (severe myoclonic epilepsy of infancy) is a rare, severe, childhood-onset, epileptic encephalopathy. Most patients with DS have a loss-of-function mutation in the voltage-gated sodium channel α1 gene (*SCN1A* gene); most of them are de novo mutations. Dravet syndrome is characterized by prolonged seizures, often triggered by fever or other quick changes in body temperature. The seizure burden is high with different seizure types such as focal or generalized seizures (absences, tonic atonic, myoclonic, tonic-clonic) and status epilepticus. Psychomotor delay and behavioral disturbances are common. The first randomized, double-blind, placebo-controlled trial of CBD in DS (GWCARE1b) was carried out in 120 children and adolescents using 20 mg/kg/day of CBD. Efficacy was assessed by comparing a 14-week treatment period with a baseline period. The median reduction in convulsive seizures was 38.9% vs 13.3% (adjusted median difference 22.8, $p = 0.01$). Responder rates were 42.6% vs 27.1% ($p = 0.08$) for convulsive seizures. For all seizures, the adjusted median difference was 19.2%, being significant ($p = 0.03$). Adverse events occurred often in the CBD group (93%) as well as in the placebo group (75%), most of the AEs were moderate or mild. Serious AEs were more common in the CBD group (16% vs 5%). Common side effects were somnolence (36% vs 10%), diarrhea (31% vs 10%), decreased appetite (28% vs 5%), and fatigue (20% vs 3%). The withdrawal rate was higher as well (13% vs 2%) [14]. A second double-blind, placebo-controlled, randomized trial investigated 10 and 20 mg/kg/day of CBD (GWPCARE2) in 199 children and adolescents using a similar protocol. Median convulsive seizure reduction was 48.7% in the CBD 10-mg/kg/day group; 45.7% in the 20-mg/kg/day group; and 26.9% in the placebo group. Responder rates were 43.9%, 49.3%, and 26.2%, respectively. Adverse events were common in all groups (87.5%, 89.9%, and 89.2%), 92% of the AEs were judged to

be mild or moderate. The most common side effects were decreased appetite, diarrhea, somnolence, pyrexia, and fatigue. A higher incidence of AEs, such as somnolence, rash, and pneumonia, was found when co-medicating with clobazam (CLB). Liver enzyme elevation (more than three times) was found in 12% of the CBD-treated patients, all of them in co-medication with valproate [15].

Lennox–Gastaut syndrome is an epileptic encephalopathy characterized by severe cognitive impairment, multiple seizures types, and abnormal electroencephalogram patterns with slowing and slow-spike and wave complexes. The incidence is about two per 100,000 and the etiology varies. The seizure burden is high and most of the patients experience drop attacks, which are a major problem because of the injury risk. Two phase III studies were carried out in patients with LGS with a focus on drop seizures. Included were 225 patients in the GWPCARE3 study, randomized to CBD 10 mg/kg/day, CBD 20 mg/kg/day, and placebo groups, all of whom were severely affected with a median frequency of more than 80 per 28 days for drop seizures and higher than 160 for all seizures. About half of the patients took CLB as a co-medication. Over a 14-week treatment period, a significant reduction in drop seizures was found between the 10-mg/kg/day group (37.2%), 20-mg/kg/day group (41.9%), and the placebo group (17.2%) reaching significance; results are significant for all seizures (36.4% vs 38.4% vs 18.5.%), but not for non-drop seizures (61.1% vs 54.6% vs 34.3%). Responder rates for drop seizures were significant (36% vs 39% vs 14%). Adverse events frequently occurred in all groups (84% vs 94% vs 72%), but most of the AEs were rated mild to moderate. Common AEs were somnolence, decreased appetite, and diarrhea; however, the number of patients who withdrew from the study because of AEs was low (1.5%, 7.3%, 1.3%) [16]. A similar study, GWPCARE4, was carried out in 171 patients, 86 in the CBD 20-mg/kg/day group and 85 in the placebo group. The primary endpoint was the mean reduction in drop seizures, which was significant (43.9% vs 21.8%, $p = 0.0135$). Adverse events occurred often (86% in the CBD group vs 69% in the placebo group) with diarrhea, somnolence, pyrexia, decreased appetite, and vomiting being the most common. Withdrawal from the study because of AEs occurred more frequently in the CBD group (14%) vs 1% in the placebo group [17].

Tuberous sclerosis complex (TSC) is a rare (1:6000), autosomal, dominant, genetic disease causing benign tumors in different organs (eyes, skin, heart, kidney, lung, and brain). The severity varies widely, but most patients with TSC have epilepsy with different seizure types [18]. After pharmaceutical-grade CBD medication for 3 months, a relevant reduction in the median seizure frequency (48.8%) and responder rates (50%) were shown. The reduction was higher in the group with the CLB co-medication (58.3% vs 33.3%). Adverse events were common (66.7%): drowsiness, ataxia, and diarrhea [19]. A randomized controlled trial for seizures in TSC (GWPCARE6) randomized 224 patients to CBD 25 mg/kg/day, CBD 50 mg/kg/day, and placebo groups. The median reduction of seizure frequency was significantly greater in CBD groups (43.4 and 36.6%) than for placebo groups (20.1%). Adverse events were common (88%, 97%, 90%). Diarrhea (31%, 55%, 25%), somnolence (13%, 26%, 9%), vomiting (10%, 16%, 8%), pyrexia (19%, 16%, 8%), and decreased appetite (20%, 23%, 12%) were the most common [20]. An open-label extension of this study is currently in the recruiting phase.

As a result of the above-mentioned studies, the first plant-derived, purified, pharmaceutical-grade CBD treatment (Epidiolex®) was approved for DS and LGS by the US Food and Drug Administration in 2018 and for the same epilepsy entities in combination with CLB by the European Medicines Agency (Epidyolex®) in 2019. In 2020, approval for the treatment of patients with TSC with plant-derived, purified, pharmaceutical-grade CBD (Epidiolex®) was given by the Food and Drug Administration only for a maintenance dose of 25 mg/kg/day as a higher dose showed a negative risk-for-benefit ratio (see Table 1 for an overview of all studies).

4 Long-Term, Follow-Up Studies in DS and LGS

Up until June 2019, 681 patients were included in long-term, follow-up studies (GWPCARE5). An interim analysis of 366 patients with LGS for a median treatment duration of 38 weeks and a mean CBD dose of 23 mg/kg/day showed a sustained reduction in seizures (between 47.7% and 57.4%) across all 12-week periods. Adverse events were common (92.1%), but were rated as mild (32.5%) or moderate (43.4%), and led to the withdrawal of 9.6% of the patients. Adverse events were, as expected, diarrhea (26.8%), somnolence (23.5%), and convulsions (21.3%) [21]. For the DS group, 264 patients with a mean dose of 21 mg/kg/day and a median treatment duration of 274 days, a sustained convulsive seizure reduction (between 37.5 and 44.3%) was achieved. Again, AEs were common (93.8%), being mild (36.7%) or moderate (39%) and led to the withdrawal of 6.4% of the patients. Diarrhea (34.5%), pyrexia (27.3%), decreased appetite (25.4%), and somnolence (24.6%) were the most common AEs [22].

Longer follow-up data (up to 96 weeks) supported the long-term treatment option with a median monthly major seizure reduction of 50% and a reduction of 44% for all seizures for a group of 152 patients with DS/LGS. For 455 patients with different types of drug-resistant epilepsies, similar results were obtained [23] .

Table 1 Results of the pivotal studies on plant-derived pharmaceutical-grade cannabidiol (CBD) [Epidiolex®]

	GWPCARE1b [14]	GWPCARE2 [15]	GWPCARE3 [16]	GWPCARE4 [17]	GWPCARE6 [20]
Epilepsy syndrome	Dravet syndrome	Dravet syndrome	Lennox–Gastaut syndrome	Lennox-Gastaut syndrome	Tuberous sclerosis complex
Number of randomized patients	120	199	225	171	224
Treatment groups	20 mg/kg/d CBD	10 mg/kg/d CBD	10 mg/kg/d CBD	20 mg/kg/d CBD	25 mg/kg/d CBD
	Placebo	20 mg/kg/d CBD	20 mg/kg/d CBD	Placebo	50 mg/kg/d CBD
		Placebo	Placebo		Placebo
Reduction in seizure frequency (primary endpoint)	Convulsive seizures	Convulsive seizures	Drop seizures	Drop seizures	All seizures
	CBD: 39%	10 mg/kg/d CBD: 49%	10 mg/kg/d CBD: 37%	20 mg/kg/d CBD: 44%	25 mg/kg/d CBD: 43%
	Placebo: 13%	20 mg/kg/d CBD: 46%	20 mg/kg/d CBD: 42%	Placebo: 22%	50 mg/kg/d CBD: 37%
	($p = 0.012$)	Placebo: 27%	Placebo: 17%	($p = 0.01$)	Placebo: 20%
Responder rates (secondary endpoint)	Convulsive seizures	Convulsive seizures	Drop seizures	Drop seizures	All seizures
	CBD: 43%	10 mg/kg/d CBD: 44%	10 mg/kg/d CBD: 36%	20 mg/kg/d CBD: 44%	25 mg/kg/d CBD: 36%
	Placebo: 27%	20 mg/kg/d CBD: 49%	20 mg/kg/d CBD: 39%	Placebo: 24%	50 mg/kg/d CBD: 40%
	($p = 0.08$)	Placebo: 26%	Placebo: 14%	($p = 0.004$)	Placebo: 22%
AE (SAE)	CBD: 93% (16%)	10 mg/kg/d CBD: 88% (20%)	10 mg/kg/d CBD: 84% (19%)	20 mg/kg/d CBD: 86% (23%)	25 mg/kg/d CBD: 88% (21%)
	Placebo: 75% (5%)	20 mg/kg/d CBD: 90% (19%)	20 mg/kg/d CBD: 94% (16%)	Placebo: 69% (5%)	50 mg/kg/d CBD: 97% (14%)
		Placebo: 89% (15%)	Placebo: 72% (9%)		Placebo: 89% (3%)

Figures were rounded

AE adverse event, *d* day, *SAE* serious adverse event

5 Studies in Other Epilepsy Syndromes

Apart from the above-mentioned epilepsy syndromes, CBD was administered in several other epilepsy entities, such as Sturge–Weber syndrome [24], Doose syndrome, Aicardi syndrome, CDKL5 deficiency disorder [25], febrile infection-related epilepsy syndrome [26], and infantile spasm [27]. This led to promising results, although a final assessment of efficacy in these syndromes has yet to be determined.

6 Cognitive and Behavioral Effects of CBD

The above-mentioned studies on the long-term safety and efficacy of CBD generally report high rates of side effects in up to 90% of the patients. The most prominent problems are diarrhea and weight loss, somnolence, and seizures [21, 23, 28]. None of these studies addresses CBD effects on cognition or mood. However, Thiele et al. reported that 88% of caregivers/parents observed an improved overall condition as assessed by the global impression change score comprising but not differentiating activity limitations, symptoms, emotions, and overall quality of life [21].

Thus, so far, CBD clinical trials suggest positive effects on other rated behaviors in groups of patients who are more severely impaired and difficult to assess from a neuropsychological perspective. Explicit studies addressing formally tested cognition are sparse, but evidence from other sources is sufficient for estimating the expected psychotropic aspects of CBD for patients with epilepsy.

First of all, animal research, using different epilepsy models, explicitly addressed the impact of CBD on the behavioral comorbidities of epilepsy. Cannabidiol has positive effects on social behavior, hyperactivity, and seizures in DS mice [29], it reduced cognitive impairment [30], it increased exploratory behavior and preserved motor function and working memory when given before pilocarpine status epilepticus [31], and it showed positive effects on motor comorbidities and working memory in rats and mice [32]. These studies suggest that CBD has a positive psychotropic impact, mostly on frontal lobe-mediated behaviors. One experimental functional magnetic resonance imaging and connectivity study, which evaluated the effect of CBD on a decision task in adult patients with drug-resistant epilepsy, suggests that CBD seems to modulate frontal lobe attention control [33].

While CBD research in the 1970s dealt primarily with the antiepileptic and sedative effects of CBD, research in the 1980s and 1990s was mainly focused on its anxiolytic, antipsychotic, and motor disease effects [34]. As previously mentioned, CBD can attenuate the anxiogenic effects of Δ9-THC [35]. It seems to have anxiolytic effects,

especially with regard to generalized social anxiety disorder [36]. Cannabidiol reduced the impact of a simulated public speaking condition on social anxiety in never before treated patients with generalized social anxiety disorder to levels observed in healthy controls [37]. Cannabidiol has anxiolytic- and antidepressant-like effects, most likely via $5HT_{1A}$-mediated neurotransmission in animal models like the elevated plus maze [38], the Vogel conflict test [39], conditioned emotional responses [40, 41], or in trace fear conditioning [42]. In keeping with animal findings on fear conditioning, CBD enhances consolidation of fear extinction in humans [43].

THC can cause schizophrenic-like symptoms that can be countered by CBD [44], but recent randomized controlled trials only confirmed the safety and not the assumed positive effects of CBD on cognition or negative symptoms in schizophrenia [45, 46]. Different from CBD in schizophrenia, a larger controlled study demonstrated that endocannabinoids (anandamide and 2-arachidonoylglycerol) affected emotion regulation as assessed via several questionnaires and scales independent of whether the patients experienced mood, anxiety, and personality disorders [47].

Apart from the anxiolytic and possibly antipsychotic effects of CBD, the endocannabinoid system plays an important role in reward learning. Although the mechanism is not yet understood, CBD seems to reduce cravings and relapses in abstinent patients with addiction disorders [48]. Preclinical studies suggest therapeutic properties on opioid, cocaine, and psychostimulant addiction and preliminary evidence suggests that CBD may be beneficial in tobacco and cannabis addiction [49].

Cannabidiol itself has a significantly low abuse potential when compared with alprazolam or dronabinol and placebo in recreational polydrug users. As for cognition, CBD when compared with alprazolam had no effect on executive functions or memory [50].

In summarizing the findings of CBD on cognition and behavior, evidence from animal research, healthy subjects, and patients with epilepsy and other diseases shows that the substance is well tolerated, has a very low abuse potential, and, so far, displays no negative effects. Instead, it appears to have a positive influence on mostly frontal lobe-mediated functions such as decision making, working memory, reward learning, and emotion regulation. This appears to be a plausible explanation for the global impression of a positive behavioral change reported in the extended-use trials on CBD and should be addressed by formalized and standardized neurocognitive assessments in the future. Indeed, a very recent publication in patients with epilepsy could show that functions of selective attention and caregiver-rated behavior significantly improved, however, without being correlated with CBD dose [51].

7 Studies with Synthetic Cannabidiol

It should be noted that most studies on CBD are conducted using plant-derived CBD. Few studies exist that feature synthetic THC-free CBD and its role in epilepsy [52–55]. A recent prospective open-label study in pediatric and adult patients with epilepsy showed similar efficacy and tolerance of synthetic CBD compared to plant-derived CBD [54], thus emphasizing the assumed therapeutic similarity of synthetic and plant-derived CBD as both of them are chemically identical [56]. Supporters of plant-derived CBD promote the "entourage effect" as a synergistic interaction between the different compounds of cannabis. However, the previously mentioned studies do not support this idea. As the demand for CBD rises dramatically, synthetic CBD might be the answer owing to the possibility of almost unlimited production volume, lack of environmental impact, and clearly defined quality criteria fulfilling the established procedures of drug regulation and, therefore, health insurance reimbursement [57, 58]. However, patients strongly prefer plant-derived CBD [57].

8 Drug–Drug Interaction with a Focus on Antiseizure Drugs

Because CBD is approved for severe childhood-onset epilepsies, its use in other types of drug-resistant epilepsies will surely be considered, though use has to be viewed as "off-label". Therefore, it is very likely that it will be administered to patients with a high drug load and polypharmacy. Hence, drug–drug interactions must be considered thoroughly and

Table 2 Drug–drug interactions

Drug	Effect of CBD on plasma concentration	Effect on CBD plasma concentration
Brivaracetam	↑	n.a.
Clobazam	↑/↔	↔ (but 7-OH-CBD ↑)
n-Methylclobazam	↑↑	n.a.
Eslicarbazepine acetate	↑	n.a.
Levetiracteam	↔	n.a.
Rufinamide	↑	n.a.
Stiripentol	↔	↑
Topiramate	↑/↔	n.a.
Valproate	↔	↔
Zonisamide	↑	n.a.

CBD cannabidiol, *n.a.* not available, ↑ elevation of plasma concentration, ↔ no change in plasma concentration

possible side effects must be monitored carefully (see drug-interaction overview in Table 2).

Clobazam is a first-line treatment drug for DS and is often used for LGS or other drug-resistant epilepsies. Clobazam is metabolized by cytochrome P450 (CYP)3A4 and CYP2C19 to its active metabolite *N*-methylclobazam (N-CLB), which is then further metabolized by CYP2C19 [59]. Being a strong inhibitor of CYP2C19, CBD has little effect on CLB and a far greater effect on *N*-CLB blood levels in healthy volunteers [60] as well as patients with epilepsy [61, 62]. Clobazam increases the active metabolite of CBD 7-hydroxy-cannabidiol without a significant increase of CBD [60]. A CBD-associated increase of *N*-CLB levels is associated with increased side effects such as sedation, somnolence, or fatigue.

In clinical studies on efficacy and safety, between 47 and 68% of the participants were taking co-medication with CLB. Considering the above-mentioned interaction between both substances, further meta-analyses were conducted. The combination of CBD and CLB was associated with a higher burden of side effects, which can, to some extent, be avoided by tapering down one of them. A meta-analysis proved the efficacy of CBD with and without concomitant CLB [63, 64], synergistic effects of CBD and CLB are discussed, and the clinical impact of the interaction between CLB and CBD is still the focus of actual investigation.

Valproate (VPA) is a first-line treatment for DS as well as LGS. It is common knowledge that VPA inhibits liver enzymes and this should always be taken into consideration for epilepsy treatment. Introducing CBD to VPA medication does not affect the pharmacokinetics of VPA in patients with epilepsy [62]. Valproate does not affect the pharmacokinetics of CBD, and for its metabolite 7-COOH-CBD, the increase is small and therefore clinically irrelevant [60]. Nevertheless, the above-mentioned pivotal studies showed that after CBD was introduced, the liver enzyme elevation was higher for patients taking VPA, which makes careful monitoring necessary [14–17].

Stiripentol is a newer antiseizure drug that may be given as a second-line adjunctive therapy in combination with CLB and VPA for refractory generalized tonic-clonic seizures in patients with DS whose seizures are not adequately controlled with CLB and VPA. Efficacy was shown in randomized controlled trials and maintained in the long-term follow-up. Side effects (ataxia, drowsiness, reduced appetite, irritability) were common and call for a reduction of the drug. Stiripentol is a strong inhibitor of several CYP enzymes (e.g., CYP2C19, CYP3A4), thus leading to increased plasma concentrations of other antiseizure drugs that are metabolized by those enzymes. Clobazam and NCLB levels increase when introducing stiripentol, and vice versa a CLB introduction increases stiripentol levels [65, 66], which can exaggerate side effects. For its special indication, stiripentol is a potential partner of CBD in the treatment of DS. Stiripentol seems not to change CBD exposure, but causes a small decrease in CBD metabolites, whereas CBD led to a small increase of stiripentol in healthy subjects [60]. A phase II study in refractory patients with epilepsy confirms a slight increase of stiripentol when introducing CBD [67], while other investigators did not report these effects [62]. Interestingly, an elevation of N-CLB by CBD did not occur in the presence of stiripentol and suggests stiripentol had maximally inhibited CYP2C19 [62].

Cannabidiol to some degree may also increase the blood concentrations of several antiseizure drugs such as zonisamide, topiramate, eslicarbazepinacetate, and rufinamide [68], which however is not supposed to be clinically relevant. Other investigators report no changes on topiramate by CBD [62]. In a small number of patients, an increase of brivaracetam blood concentrations was measured after CBD was introduced, with two of five patients experiencing self-limiting side effects [69]. In two studies, CBD did not influence levetiracetam [62, 70].

9 Pitfalls and Challenges

Demand for CBD is rising owing to the above-mentioned reports in social media as well as aggressive marketing strategies. Because of the overwhelming supply available over the internet or in specialist shops, CBD is easy to purchase in any preparation and dosage form. However, these non-pharmaceutical products are not under the same legal scrutiny as pharmaceutical-grade products, hence the quality and quantity of CBD remain unclear. Inaccurate labeling with under- and overdosing of CBD and unexpected co-contents were detected in products with specified contents [71], which might lead to unforeseen conditions. Self-medication is often viewed as harmless and a complementary medicine; however, drug interactions are well known [72]. Self-medication with CBD is known for patients with epilepsy and this is supported by easy access and non-prescription availability. Patients are highly expectant with regard to the efficacy of CBD treatment in epilepsy and the supposed additional benefits including relief in other health conditions and a general feeling of well-being. Acceptance of side effects is high as seen in the pivotal studies and additional surveys. This reflects the high expectation patients have with regard to symptom relief and the prospect of "salvation", which patients with epilepsy assign to a supposedly non-harmful, plant-derived drug [57].

Cannabidiol is, at least in the epilepsy market, a cost-intensive medication, for example, the estimated cost in Germany per gram is €100–€200, depending on the quality. Depending on the dose and the patient's body weight, the monthly costs for an adult patient with epilepsy are about

€3000, in contrast to the average monthly costs arising from anticonvulsant therapy, for example, costs per patient in a German tertiary epilepsy center are about €262 [73]. Presently, CBD treatment of epilepsies that are not LGS or DS (or TSC in the USA) is difficult and needs a special and explicit assumption of cost by the health insurance company. In Table 3, we provide a synopsis of recommendations and personal practice for CBD treatment derived from the above-mentioned topics to provide the treating physician with the necessary information for treating patients with epilepsy.

Table 3 Practical use of cannabidiol (CBD). Synopsis of recommendations and personal practice

	DS	LGS	TSC	DRE
Approval				
FDA	In label (≥1 y of age)	In label (≥1 y of age)	In label (≥1 y of age)	Off label
EMA	In label [with CLB co-medication] (≥2 y of age)	In label [with CLB co-medication] (≥2 y of age)	Off label	Off label
Before starting CBD				
Administration			For off-label prescription: check insurance refund	
Clinical data	Seizure burden			
	Cognitive and behavior function			
Laboratory	Serum transaminases, total bilirubin (obligatory), blood count, creatinine (recommended)			
	Plasma concentrations of concomitant antiseizure medication			
Starting CBD				
Starting	Starting dose 2.5 mg/kg, twice daily: 5 mg/kg			Starting dose 1.5 mg/kg, twice daily: 3 mg/kg[a]
Titration	After 1 wk 5 mg/kg, twice daily: 10 mg/kg			After 2 wk, 2.5 mg/kg, twice daily: 5 mg/kg[a]
	Based on individual response and tolerability taper up		Increase dose weekly by 2.5 mg/kg	Increase dose every 2 wk by 2.5 mg/kg[a]
Maximum recommended maintenance dosage	20 mg/kg/d		25 mg/kg/d	20 mg/kg/d[a]
Laboratory monitoring	Starting CBD: after 1 mo, 3 mo, 6 mo, thereafter periodically: serum transaminases, total bilirubin (obligatory), plasma concentrations of antiseizure co-medication (recommended)			
	Or as clinically indicated: serum transaminases, total bilirubin (obligatory), plasma concentrations of antiseizure co-medication (recommended)			
	Change in CBD dosage: after 1 mo of serum transaminases, total bilirubin (obligatory)			
	Addition or change of medications having an impact on the liver: after 1 mo of serum transaminases, total bilirubin			
	Baseline elevated liver enzymes: monthly[a] or as clinically indicated: serum transaminases, total bilirubin (obligatory)			
	Co-medication with VPA: monthly[a] or as clinically indicated serum transaminases, total bilirubin			
Withdrawal of CBD				
Side effects	Time schedule depending on severity of side effects			
	For intolerance of CBD by CNS side effects (e.g., dizziness, vertigo, somnolence): dosage adjustment (CBD or CLB or co-medication)			
Missing efficacy	Time schedule depending on seizure burden			
Elevated liver enzymes	Caution: > 3-fold ULN and bilirubin > 2-fold ULN: discontinuation of CBD			
	Caution: > 5-fold ULN: discontinuation of CBD			

CLB clobazam, *CNS* central nervous system, *d* day, *DRE* drug-resistant epilepsy, *DS* Dravet syndrome, *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *LGS* Lennox–Gastaut syndrome, *mo* month, *TSC* tuberous sclerosis complex, *ULN* upper limit of normal, *VPA* valproate, *wk* week, *y* year

[a]Personal practice (not explicitly recommended by manufacturer or legally approved)

10 Conclusions

Cannabidiol is an interesting, but very expensive treatment option for drug-resistant epilepsy. Several studies showed promising results for treating special epileptic encephalopathies, but the efficacy for treating epilepsy in general is still under investigation. Though high rates of side effects have been reported, withdrawal is rare and there is growing evidence of a positive influence of CBD on behavior and cognition. Difficulties involving CBD treatment are costs, drug–drug interactions, as well as the complex and emotionally triggered preconception reflecting the ideas patients and caregivers have regarding CBD as a cannabis-derived option.

Declarations

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