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Epilepsy (E Waterhouse, Section Editor)

Cannabinoids for the Treatment of Epilepsy: a Review

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Abstract

Purpose of review Treatment-resistant epilepsy (TRE) is associated with severe morbidity and mortality and affects over 30% of epilepsy patients. Despite advances in epilepsy management over the last 30 years, this rate has largely remained unchanged. Through a largely patient driven movement and despite federal regulations, cannabidiol (CBD) emerged as a candidate drug for improving the management of treatment-resistant epilepsies. This review highlights the available research on CBD and its therapeutic role in the treatment of TREs.
Recent findings Randomized controlled trials have established CBD as an add-on treatment option for the management of seizures in Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS), and there is a growing body of additional literature supporting CBD's use as an add-on therapy in other TREs. Several studies have shown CBD to be a safe anti-seizure medication with dose-dependent mild-moderate adverse events which resolve with treatment de-escalation. CBD does affect toxicity with other anti-seizure medications including clobazam and valproate.
Summary CBD is a safe and efficacious adjunctive therapy in the management of treatment-resistant epilepsies.

Introduction

The World Health Organization recognizes epilepsy as the most common chronic neurologic disorder worldwide, affecting more than 50 million people. Treatment-resistant epilepsy (TRE) is defined as failure of seizure remission after at least two adequate anti-seizure medications [1]. Over 30% of people with epilepsy will

continue having seizures despite medication therapy. Over the past 30 years, there have been advances in drug availability, the advent of many anti-seizure medications with unique mechanisms, and advances in diet and surgical interventions, but the rate of TRE has remained unchanged [2–4]. TRE is associated with increased morbidity, often from disabling medication side effects, increased mortality, and worse quality of life [5–9]. These facts have pushed the scientific community to continue exploring different options for safer and more effective anti-seizure therapies.

Descriptions of cannabis use for the treatment of seizure can be found dating back thousands of years on Sumerian tablets and again over one thousand years ago from Middle Eastern scholar al-Mayusi [10, 11]. Western medicine began exploring the therapeutic effects of cannabis in the nineteenth century. Anecdotal reports of successful treatment of seizures were noted by physicians of the time including William O'Shaughnessy, JR Reynolds, and William Gowers [12–14]. The current wave of scientific research began in the 1960s when scientists were able to isolate tetrahydrocannabinol (THC), the main psychoactive component of cannabis, and cannabidiol (CBD), the main non-psychoactive combound of cannabis. In addition, endogenous brain cannabinoids and their associated cannabinoid receptors (CB1) were discovered [15]. This early work leads to the discovery of the endogenous cannabinoid-signaling system in the 1990s and began the current wave of medical research surrounding cannabis derived compounds and their potential medicinal benefits [16].

Despite federal regulations on *Cannabis* species and the compounds derived, many people with TREs sought CBD-enriched cannabis and reported anecdotal evidence of seizure reduction [17]. This culminated with the story of Charlotte Figi, a child a pathogenic *SCN1A* mutation causing Dravet syndrome, who saw a dramatic improvement in seizure burden and development after initiating adjunctive therapy with a CBD-enriched cannabis which was later coined "Charlotte's Web" [18]. Media attention assisted a largely patient based movement seeking CBD-enriched products for the treatment of TREs. Several states made lawful provisions allowing medical use and additional companies began producing these products. Unfortunately, in 2015, an initial US Food and Drug Administration (FDA) analysis showed that 6 of 18 over-the-counter CBD preparations contained no cannabinoids [19]. The FDA has continued sending yearly warning letters regarding the purity of cannabidiol-related products.

This largely patient driven movement led to the development of Epidiolex (Greenwich Biosciences, London, UK), an FDA-approved product containing 99% pure oral CBD extract which was listed into schedule V of the Controlled Substance Act in 2018. The development and approval of this medication have allowed for investigators to provide a controlled product while studying the effects of CBD on seizures. Many of the completed and ongoing clinical trials have used Epidiolex. This article will briefly review what is known of the mechanism of action and explore the results of open-label studies and clinical trial data available for CBD and its role in the treatment of epilepsy.

Mechanism of action and interactions

The exact mechanism by which CBD exerts its anti-seizure properties has not been fully elucidated. CBD has a wide range of effects which are thought to decrease excess neuronal activity [20]. Unlike THC, CBD has a relatively low affinity for cannabinoid type 1 and 2 receptors (CB1R & CB2R) and may actually work as an antagonist, or in the case of CB1R an inverse agonist, at these receptors [21]. Similar to zonisamide and ethosuximide, it has been shown that CBD blocks human T-type voltage-gated calcium channels [22]. In addition, CBD is thought to modulate calcium channels by acting as an agonist at delta-tetrahydrocannabinolic acid (TRP) channels, particularly TRPV1, although it is unknown if this adds to CBD's anti-seizure effects [23]. Laboratory models have shown an ability to block voltage-gated sodium channels (VGSC) including the mutated channels seen in some epileptic encephalopathies including Dravet

syndrome, which is a theoretical reason CBD may work in these syndromes [24]. CBD also has the ability to modulate various additional receptors. Similar to fenfluramine, CBD may modulate serotonin release through actions at 5-HT_{1A} and 5-HT_{2A} receptors. Other receptors which CBD interacts include G-coupled receptor protein 55, adenosine 1 and 2 receptors, voltage-dependent anion-selective channel protein 1, and tumor necrosis factor alpha but at this time, it is unknown what role, if any, CBD's interaction with these receptors plays in its anti-seizure properties [23].

CBD is also a known inhibitor of the cytochrome P450 (CYP450) system, particularly the CYP3A4 and CYP2C19 enzymes which are responsible for its metabolism. While this interaction does not play a role in its anti-seizure effects, CYP450 is responsible for the hepatic metabolism of many drugs, including several anti-seizure medications, and causes the impaired metabolism of clobazam [25].

CBD and Epilepsy

At the time of this review was written (July 2019), 10 interventional clinical trials regarding CBD and its role in the treatment of epilepsy were completed (Table 1) according to www.clinicaltrials.gov. Sixteen clinical trials were active and either recruiting or had completed enrollment. The following sections will review the available published clinical data regarding CBD and its role in the management of epilepsy. All studies reviewed below used CBD as an adjunctive therapy.

Randomized Placebo-Controlled Trials for Epilepsy

GWPCARE1 Part A (NCT02091206) focused on the safety and preliminary pharmacokinetic data was evaluated in a double-blind trial involving patients with Dravet syndrome in the clinical trial NCT0291206 [26]. Thirty-four patients were randomized to 5, 10, or 20 mg/kg/day of CBD or to a placebo group. CBD exposure was found to increase the clobazam metabolite N-desmethylclobazam but had no effect on any other investigated anti-seizure drug (valproate, levetiracetam, topiramate, or stiripentol). Treatment-emergent adverse effects experienced by more than 3 patients included pyrexia, somnolence, decreased appetite, sedation, vomiting, ataxia, and abnormal behavior. A dose relationship was only observed for decreased appetite. Adverse events caused two patients to withdraw from the study including a patient (10 mg/kg/day group) with fever and a maculopapular rash and a patient (20 mg/kg/day group) with elevated transaminases meeting withdrawal criteria which was set as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 8 × the upper limit of normal which resolved after discontinuation from the trial. GWPCARE1 Part B (NCT02091375) evaluated CBD efficacy in 120 children and young adults with Dravet syndrome over a 14-week treatment period [27••]. Convulsive seizures significantly decreased from 12.4 to 5.9 per month (median decrease of 38.9%) in the treatment group when compared with a 14.9 to 14.1 drop in the placebo group ($p = 0.01$). Frequency in total seizures of all types was also significantly reduced in the CBD group (– 19.2%, $p = 0.03$). Adverse events were reported in > 10% of patients receiving CBD included diarrhea (31%), vomiting (15%), fatigue (20%), pyrexia (15%), decreased appetite (28%), convulsions (11%), lethargy (13%), and somnolence (36%).

Table 1. Completed interventional clinical trials of cannabidiol in the treatment of epilepsy

NCT number	Title	Conditions	Interventions	Characteristics	Outcome measures	Dates
NCT02987114	A study to evaluate the safety, tolerability, and efficacy of oral administration of PTL 101 (cannabidiol) as an adjunctive treatment for pediatric intractable epilepsy	Intractable epilepsy	Drug: PLT101	Study type: interventional Phase: phase 2 Industry-funded Sponsored by PhytoTech Therapeutics, Ltd	Incidence of study treatment related adverse events (AEs) Percent change in mean countable monthly seizure frequency Incidence of all AEs Assessment of Caregiver Global Impression of Improvement using a 5-point rating scale Assessment of Caregiver Global Impression of Seizure Severity using a 5-point rating scale	Study start: February 13, 2017 Primary completion: June 28, 2018 Study completion: June 28, 2018 Results first posted: no results posted Last update posted: September 6, 2018
NCT02544763	A randomized controlled trial of cannabidiol (GWP42003-P, CBD) for seizures in tuberous sclerosis complex (GWPCARE6)	Tuberous sclerosis complex seizures	Drug: GWP42003-P Drug: placebo	Study type: interventional Phase: phase 3 Sponsored by GW Research Ltd	Change in seizure frequency Number of treatment responders Number of participants with worsening, no change, or improvements in seizure frequency Change in composite focal seizure score Change in number of seizure-free days Change in number of seizures by subtype Change in number of infantile/epileptic spasms Change in use of rescue medication Change in number of episodes of status epilepticus Change in duration of seizures by subtype 11 additional measures	Study start: April 6, 2016 Primary completion: January 22, 2019 Study completion: February 26, 2019 Results first posted: no results posted Last update posted: June 7, 2019
NCT02324673	Cannabidiol oral solution in pediatric participants with treatment-resistant seizure disorders	Seizures	Drug: cannabidiol oral solution	Study type: interventional Phase: phase 1 and phase 2 Industry-funded Sponsored by INSYS Therapeutics Inc.	Maximum plasma concentration (Cmax) for cannabidiol and metabolite 7-hydroxy (7-OH) cannabidiol Cmax for cannabidiol and metabolite 7-OH cannabidiol Dose-normalized Cmax (Cmax/D) for cannabidiol and metabolite 7-OH cannabidiol	Study start: April 13, 2015 Primary completion: May 9, 2016 Study completion: May 9, 2016 Results first posted: June 23, 2017 Last update posted: June 23, 2017

Table 1. (Continued)

NCT number	Title	Conditions	Interventions	Characteristics	Outcome measures	Dates
					Time to Cmax (Tmax) for cannabidiol and metabolite 7-OH cannabidiol Half-life (t1/2) for cannabidiol for participants #2 years of age Elimination rate (lambda-z[#z]) for cannabidiol and metabolite 7-OH cannabidiol for participants #2 years of age Oral clearance (CL/F) for cannabidiol for participants #2 years of age Volume of distribution Of cannabidiol for participants #2 years of age Area under the plasma-concentration time curve from 0 to 12 h post-dose [AUC(0–12)] for cannabidiol and metabolite	
NCT02564952	An open-label extension study to investigate possible drug-drug interactions between clobazam and cannabidiol	Epilepsy	Drug: GWP42003-P Drug: clobazam	Study type: interventional Phase 2 Industry-funded Sponsored by GW Research Ltd	Number of participants who experienced severe OLE-emergent AEs	Study start: March 11, 2016 Primary completion: June 7, 2017 Study completion: June 7, 2017 Results first posted: September 11, 2018 Last update posted: September 11, 2018
NCT02318602	Cannabidiol oral solution as an adjunctive treatment for treatment-resistant seizure disorder	Seizures	Drug: cannabidiol oral solution	Study type: interventional Phase 3 Industry-funded Sponsored by INSYS Therapeutics Inc.	Percentage of participants with adverse events percentage of participants with serious adverse events Percentage of participants with clinically significant change from baseline in electrocardiogram findings Percentage of participants with clinical significant change from baseline in vital signs Change from baseline in trough plasma levels of cannabidiol and its 7-OH metabolite Vinland Adaptive Behavior Scales (VABS) Number of participants with a positive response on the Columbia-Suicide Severity Rating Scale (C-SSRS)	Study start: January 8, 2016 Primary completion: June 22, 2017 Study completion: June 22, 2017 Results first posted: July 25, 2018 Last update posted: July 25, 2018

Table 1. (Continued)

NCT number	Title	Conditions	Interventions	Characteristics	Outcome measures	Dates
NCT02565108	A randomized controlled trial to investigate possible drug-drug interactions between clobazam and cannabidiol	Epilepsy	Drug: GWP42003-P 20 mg/kg/day dose Drug: placebo Drug: clobazam	Study type: interventional Phase 2 Industry-funded Sponsored by GW Research Ltd	Pharmacokinetics (PK): maximum measured plasma concentration (Cmax) of CLB and N-CLB with GWP42003-P treatment, days 1 and 33 PK: time to maximum plasma concentration (Tmax) of CLB and N-CLB With GWP42003-P treatment, days 1 and 33 PK: area under the plasma concentration time curve over a dosing interval, where tau is the dosing interval (AUCtau) of CLB and N-CLB with GWP4002003-P treatment, days 1 and 33 PK: geometric mean ratios of CLB and N-CLB for Cmax on day 33 compared with day 1 PK: geometric mean ratios of CLB and N-CLB for AUCtau on day 33 compared with day 1 Number of participants who experienced severe treatment-emergent adverse events (TEAEs)	Study start: January 20, 2016 Primary completion: July 21, 2016 Study completion: July 21, 2016 Results first posted: August 23, 2018 Last update posted: August 23, 2018
NCT02091375	Antiepileptic efficacy study of GWP42003-P in children and young adults with Dravet syndrome (GWPCARE1)	Epilepsy Dravet syndrome	Drug: GWP42003-P 20 mg/kg/day dose Drug: placebo controlled	Study type: interventional Phase 3 Industry-funded Sponsored by GW Research Ltd	Percentage change from baseline in convulsive seizure frequency during the treatment period number of participants with a 50% reduction from baseline in convulsive seizure frequency during the treatment period Number of participants with a 25%, 75%, or 100% reduction from baseline in convulsive seizure frequency during the treatment period Percentage change from baseline in non-convulsive seizure frequency during the treatment period Caregiver Global Impression of Change In Seizure Duration (CGICSD) Number of participants using rescue medication Number of participants with inpatient Hospitalizations due to epilepsy Change from baseline in sleep disruption 0 to 10 numerical rating scale (0 to 10 NRS) score	Study start: March 30, 2015 Primary completion: November 26, 2015 Study completion: November 26, 2015 Results first posted: July 20, 2018 Last update posted: August 27, 2018

Table 1. (Continued)

NCT number	Title	Conditions	Interventions	Characteristics	Outcome measures	Dates
					Change from baseline in Epworth Sleepiness Scale (ESS) score Change from baseline in Quality Of Life In Childhood Epilepsy (QOLCE) score	
NCT02224690	A study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults (GWPCARE4)	Epilepsy Lennox-Gastaut syndrome	Drug: GWP42003-P 20 mg/kg/day dose Drug: placebo	Study type: interventional Phase 3 Industry-funded Sponsored by GW Research Ltd	Percentage change from baseline in drop seizure frequency during the treatment period Number of participants with a 50% reduction from baseline in drop seizure frequency during the treatment period Percentage change from baseline in total seizure frequency during the treatment period Subject/Caregiver Global Impression of Change Assessment (S/CGIC)	Study start: April 28, 2015 Primary completion: March 18, 2016 Study completion: March 18, 2016 Results first posted: July 27, 2018 Last update posted: July 27, 2018
NCT02091206	A dose-ranging pharmacokinetics and safety study of GWP42003-P in children with Dravet syndrome (GWPCARE1)	Epilepsy Dravet syndrome	Drug: GWP42003-P 5 mg/kg/day, 10 mg/kg/day, and 20 mg/kg/day Drug: placebo control	Study type: interventional Phase 2 Industry-funded Sponsored by GW Research Ltd	Number of participants who experienced severe treatment-emergent adverse events (TEAEs) Area under the concentration-time curve calculated to the last observable concentration at time T (AUC0-t) for CBD and its metabolites at days 1 and 22 Mean percentage change from baseline to end of treatment in plasma clobazam (CLB) and N-desmethylclobazam (NCLB) concentrations	Study start: October 22, 2014 Primary completion: March 9.2015 Study completion: March 9, 2015 Results first posted: July 19, 2018 Last update posted: August 24, 2018
NCT02224560	Efficacy and safety of GWP42003-P for seizures associated with Lennox-Gastaut syndrome in children and adults (GWPCARE3)	Epilepsy Lennox-Gastaut syndrome	Drug: GWP42003-P Drug: placebo control	Study type: interventional Phase 3 Industry-funded Sponsored by GW Research Ltd	Percentage change from baseline in drop seizure frequency during the treatment period Number of participants with a #50% reduction from baseline in drop seizure frequency during the treatment period Percentage change from baseline in total seizure frequency during the treatment period Subject/Caregiver Global Impression of Change (S/CGIC) assessment	Study start: June 8, 2015 Primary completion: May 19, 2016 Study completion: May 19, 2016 Results first posted: July 27, 2018 Last update posted: July 27, 2018

Elevated liver transaminases were noted in 12 patients (11 in CBF group) of which all were taking concomitant valproate.

Data from two separate randomized placebo-controlled trials (GWPCARE3 NCT02224560 & GWPCARE4 NCT02224690) for patients with Lennox-Gastaut syndrome (LGS) were published in 2018. GWPCARE3 focused on the efficacy and safety of CBD as a treatment for drop seizures in patients with LGS [28••]. A total of 225 participants aged 2 to 55 years old were randomized to 10 mg/kg/day ($n = 73$), 20 mg/kg/day ($n = 76$), or placebo groups ($n = 76$) and were monitored over a 14-week period. A significant decrease in drop seizure frequency was observed (20 mg/kg/day = 41.9% ($p = 0.05$), 10 mg/kg/day = 37.2% ($p = 0.002$), placebo = 17.2%) in both treatment arms. Higher doses were observed to have more frequent adverse events. More than 10% of patients reports of somnolence (21–30%), decreased appetite (16–26%), diarrhea (10–15%), and vomiting (6–12%). Elevated liver aminotransferase concentrations (> 3 × upper limit of normal) were observed in 14 patients (9%) most of which were in the 20 mg/kg/day group and receiving concomitant valproate. GWPCARE4 also investigated CBD as add-on therapy for drop seizures in patients with LGS [29]. A total of 171 patients were assigned to CBD ($n = 86$) or placebo ($n = 85$). A 43.9% reduction in monthly drop seizures was noted in the treatment group vs 21.8% in the placebo group ($p = 0.0135$). Similar adverse events were observed including diarrhea, somnolence, decreased appetite, and vomiting.

Open-Label Interventional Trials

Early data from an open-label state-sponsored safety study on pharmaceutical grade CBD (Epidiolex) use in a mix of 51 adult and pediatric patients with TRE was published in 2016. Patients enrolled in the study had failed at least 4 different anti-seizure medications and were experiencing at least 4 countable seizures per month. After an initial seizure baseline averaged over 3 months, CBD was initiated at 5 mg/kg/day with adjustments biweekly to a maximum of 25 mg/kg/day. Forty-nine percent were labeled good responders (> 50% seizure reduction), no difference between adult and pediatric response rates were noted, and two patients experienced seizure freedom. Importantly, seizure reduction was shown to be sustained over the 6 month study [30].

In the same year, Devinsky et al. published their results on a prospective, open-label, expanded access trial at 11 independent epilepsy centers in the United States. After an enrollment period of 4 weeks to establish a baseline, patients aged 1–30 years old with intractable childhood-onset epilepsy were given CBD beginning at 2–5 mg/kg/day titrating weekly to intolerance or a maximum dose of 25 mg/kg/day, although at some institutions, doses as high as 50 mg/kg/day were used. Analysis was performed after a 12 week intervention period. Two hundred fourteen were enrolled with 162 included in the safety analysis and 137 included in the intention-to-treat efficacy analysis. One hundred twenty-eight reported adverse events (79%). Somnolence (41; 25%), decreased appetite (31; 19%), diarrhea (31; 19%), and fatigue (21; 13%) were the most common reported adverse events. Somnolence was noted in a higher percentage (51%) of patients taking clobazam and CBD then those treated with other concomitant anti-seizure medications (21%) (OR of 3.87, 95% CI 1.9–7.9). Treatment-emergent serious adverse events were reported in 48 (30%),

including one death which was felt to be unrelated to the study drug. Those noted in > 1% of the patients included status epilepticus (9; 6%) and diarrhea (3; 2%). No correlation between CBD dose and number of reported adverse events or reported somnolence was noted; however, patients taking more than 15 mg/kg/day were more likely to report diarrhea or related side effects. The primary outcome measure reported was frequency of motor seizures per month. After the 12-week intervention period, the mean change in reported monthly motor seizures was – 36.5% with 5 patients (4%) reporting complete motor seizure resolution [31].

University of Alabama Birmingham completed a single-center open-label prospective study on CBD and treatment-resistant epilepsy with 72 children and 60 adult participants which evaluated adverse events, seizure severity, and seizure frequency using doses titrated from 5 mg/kg/day to a maximum of 50 mg/kg/day with data analysis at 12, 24, and 48 weeks [32]. Study retention at 1 year was 77%. Seizure severity, as monitored using the Chalfont Seizure Severity Scale, significantly decreased at 12 weeks (80.7 at baseline to 39.2; $p < 0.0001$) and remained stable over remainder of trial period. Mean biweekly seizure frequency decreased from 144.4 to 52.2 ($p = 0.01$) at 12 weeks and remained stable over trial period. At 12-week interval, 6.2% of participants reported 100% seizure freedom (8.7% children, 3.3% adults). At 48-week re-evaluation, 3.3% of participants reported 100% seizure freedom (0% children, 5.9% adults). Adverse events were monitored using the Adverse Event Profile (AEP). A significant decrease from baseline was noted at 12 weeks ((40.8 to 33.2, $p < 0.0001$) and remained stable over the 48-week period.

Expanded access programs have provided some long-term efficacy and safety data regarding CBD use in treatment-resistant epilepsies in children and adults. Analysis of a data set including 607 mixed pediatric and adult patients at 25 enrolling sites from 2014 to 2016 was published in 2018 [33•]. Of the 607 patients, 146 (24%) withdrew most often due to lack of efficacy (15%). Thirty-two (5%) withdrew due to adverse events. The most common adverse events were diarrhea (22%) and somnolence (22%). Median CBD dose was 25 mg/kg/day and median treatment duration was 48 weeks. Median monthly convulsive seizures were reduced by > 50% and total seizures were reduced by 48% at 12 weeks. Fifty-two percent, 31%, and 11% achieved a > 50%, > 75%, and 100% reduction in convulsive seizures respectively at 12 weeks with similar results through total 96 weeks. Further data was provided through an expanded access program in the USA including 26 pediatric patients aged 1–17 years old with TRE [34]. Adverse events were reported in > 80% of patients (21 of 26) including reduced appetite ($n = 10$), diarrhea ($n = 9$), and weight loss ($n = 8$). Increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were noted in 3 patients taking concomitant valproate. Serious adverse events included status epilepticus ($n = 3$), catatonia ($n = 2$), and hypoalbuminemia ($n = 1$). At 24 months, 26 (~ 35%) continued CBD as an adjunctive therapy. More than 25% had a sustained > 50% reduction in motor seizures and 11.5% reported complete seizure freedom.

Patients with Dravet syndrome who completed GWPCARE 1 parts A or B (NCT02091206) or GWPCARE2 (NCT02224703) were invited to enroll in a long-term open-label extension (GWPCARE5, NCT02224573). Interim analysis of safety, efficacy, and patient-reported outcomes has been published [35]. Two hundred and sixty-four of 278 patients who completed the original

randomized trials enrolled in the open-label extension. A median dose of 21 mg/kg/day was used. Adverse events were reported in > 90% of patients which were mostly labeled mild or moderate and were most commonly diarrhea (34.5%), pyrexia (27.3%), decreased appetite (25.4%), and somnolence (24.6%). Only 17 patients (6.4%) discontinued use of CBD due to adverse effects. Similar to other studies, increases in ALT and AST (> 3 × upper limited of normal) were noted in patients taking valproate (22 of 128 patients). Eighty-five percent of patients or caregivers reported improvement in overall condition after 48 weeks (total of 89 patients had completed 48 weeks of treatment at interim analysis).

Similar results were noted in a separate open-label expanded access study of the effects of CBD in patients with tuberous sclerosis complex (TSC) and TRE [36]. After an initial 1-month baseline, 18 patients with TSC and TRE were given CBD starting at 5 mg/kg/day and titrated to a maximal dose of 25–50 mg/kg/day based on tolerability. Analysis was performed at intervals over a 12-month period. Twelve of 18 patients experienced at least one adverse event, most commonly drowsiness (8; 44%), ataxia (5; 28%), and diarrhea (4, 22%). After 3 months of treatment, the median percent change in total reported weekly seizure frequency of all seizure types decreased by 48.8% and similarly to the Devinsky study, a higher 50% responder rate was noted in patients taking concomitant clobazam (58.2% vs 33.3%).

Additional information has been published regarding other epileptic encephalopathies including CDKL5 deficiency, Aicardi, Doose, and Dp15q syndromes. An open-label compassionate use study in these patients aged 1–30 years old (CDKL5 $n = 20$, Aicardi Syndrome $n = 19$, Doose syndrome $n = 8$, and Dup15q $n = 8$) documented a > 50% reduction in median convulsive seizure frequency at 12 and 48 weeks [37]. During this study, the most frequently reported adverse events included diarrhea (29%), somnolence (22%), fatigue (22%), and decreased appetite (20%).

An open-label case series published on children with diagnosed febrile infection-related epilepsy syndrome (FIRES) suggested CBD as a possible treatment. Seven children from 5 different centers were treated in either the acute or chronic phase of the illness. Six of 7 had improved seizure frequency, one died due to multi-organ failure secondary to isoflurane, and an average of 4 anti-seizure medications were weaned. Follow up data suggested improved outcome from the typical illness course including 5 who ambulated without assistance, 1 who walked with assistance, and 4 who were verbal [38].

Outside of seizure reduction, CBD may also have an impact on quality of life (QOL) in patients with TRE [39]. When QOLCE survey results were compared before and 12 weeks after the introduction of CBD, significant score improvements were noted in the domains of energy/fatigue ($p = 0.003$), memory (< 0.001), other cognitive functions (< 0.001), social interactions (0.003), behavior (0.001), and quality of life (< 0.001). No relationship was observed between QOLCE score changes and change in monthly seizure frequency ($p = 0.9$) or number of adverse effects ($p = 0.671$).

Other studies have looked at have suggested possible benefit in additional populations. A small study of 5 patients with Sturge-Weber syndrome and TRE noted 2 of 5 subjects after 14 weeks of treatment reported a greater than 50% reduction in seizures and an improved quality of life [40].

Additional Information on Safety and Drug-Drug Interactions

Additional articles have been published on CBD safety and its known drug-drug effects. An open-label trial using 77 healthy subjects was designed to further evaluate CBD and possible interactions with clobazam, stiripentol, and valproate serum levels [41]. CBD was found to increase N-desmethylclobazam exposure and slightly increase stiripentol exposure. Concomitant clobazam increased 7-OH-CBD metabolite exposure without a notable increase in CBD exposure. Six participants withdrew due to adverse effects, 3 with concomitant clobazam, and 3 with concomitant valproate. Five of the 6 were withdrawn due to rash with two classified as severe occurring in the concomitant clobazam group. In total, 9 (11.7%) participants experienced rash, of which 8 were thought to be drug-related. Of note, these occurred in groups with no or rapid titration of CBD dose.

Further information on drug-drug interactions was provided through open-label trials (NCT02695537 [pediatric arm] and NCT02700412 [adult arm]) [42]. In 42 children and 39 adults who received CBD doses titrated between 5 mg/kg/day and a maximum of 50 mg/kg/day significant increases in serum levels of topiramate, rufinamide, and N-desmethylclobazam, and decreases in clobazam were noted in both children and adults with increasing CBD dose. Increased serum levels of zonisamide and eslicarbazepine were noted in adults only. Higher N-desmethylclobazam levels were associated with more frequent complaints of sedation in adults. AST and ALT levels were higher in patients taking concomitant valproate.

Thirteen pediatric patients who completed an expanded access investigational study and were taking concomitant CBD and clobazam [25]. A significant increase in N-desmethylclobazam level was noted of at least 1.9 × despite reduced doses in most patients. Ten of 13 reported side effects which were most often drowsiness [6], ataxia [2], and irritability [2]. All reported side effects in this study resolved with clobazam dose adjustment, and all subjects were tolerating CBD well at week 36 of treatment.

Clinical Trials: What is on the Horizon?

We await the results of two interventional clinical trials which have been completed but have not had results posted or published which look to broaden our knowledge on CBD in the treatment of pediatric treatment-resistant epilepsy (NCT02987114) and in tuberous sclerosis (GWPCARE6, phase 3 placebo-controlled trial; NCT02544763). Several clinical trials are recruiting with goals of expanding the indication of CBD in the treatment of different forms of epilepsy and include treatment-resistant childhood absence seizures (NCT03355300 & NCT03336242). In addition to these trials, there are several domestic (USA) and international clinical trials which are active or in the recruiting phase which look to expand the data on CBD and its use in treatment-resistant epilepsies.

Additional studies are being completed which are expounding CBD's role in epileptic encephalopathies. Further information on CBD and its efficacy in DS and LGS will be published on completion of an open-label extension trial (GWPCARE5, NCT02224573) which has enrolled 681 participants in June of 2020. Several clinical trials are focusing on CBD and a possible role in the

treatment of infantile spasms (IS). A pilot clinical trial (NCT02551731) of only 9 infants with refractory infantile spasms has reported data of complete resolution of spasms in 14.3% of children after 14 days of treatment. GWPCARE7 (NCT02954887) enrolled 202 participants in a randomized controlled phase 3 trial to evaluate CBD for IS and results are not yet posted. An additional phase 3 interventional, placebo-controlled randomized trial is ongoing and the efficacy of CBD as an adjunctive initial therapy with vigabatrin for infantile spasms is scheduled to complete in December of 2019 (NCT03421496).

Conclusion

Despite an only recent FDA approval and a limited label indication for treatment of DS and LGS-associated epilepsies, CBD has a large body of evidence supporting its efficacy as an add-on therapy in all seizure types. Almost all studies discussed above have reported similar rate of seizure reduction (~ 40–50%) which appears sustained over prolonged treatment courses. A small percentage of patients using CBD as add-on therapy, up to 3–10%, may experience 100% seizure reduction.

The available safety data shows that CBD as add-on therapy is a relatively safe anti-seizure medication. Reported adverse events are mild in severity, are dose-related, and resolve with dose reduction of CBD or concomitant anti-seizure medications. These side effects include diarrhea, vomiting, decreased appetite, weight loss, somnolence, and fatigue.

While the mechanism of CBD or how it interacts with other anti-seizure medications in metabolic pathways is not fully understood, it is clear that CBD interacts with clobazam by increasing its active metabolite N-desmethylclobazam and can lead to increased somnolence and fatigue. While the increase in this metabolite may play a beneficial role in seizure reduction, reduction of concomitant clobazam often resolves somnolence and fatigue. Additionally, the combination of CBD and valproate can cause elevation of liver transaminases, notably without any effect on the levels of valproate or its metabolites, and occurs most often with high doses and rapid titration but resolves with removal or de-escalation of either medication.

The available research highlights CBD as a safe and efficacious adjunctive therapy in the management of treatment-resistant epilepsies. Further studies are ongoing which will likely broaden its FDA-approved indication in the near future. Continued clinical trials are needed to understand further CBD's role in the management of epilepsy.

Compliance with Ethical Standards

Conflict of Interest

Dr. Galan declares that he has no conflict of interest. Dr. Miller reports grants, personal fees, and non-financial support from Greenwich Biosciences during the conduct of the study; personal fees and non-financial support from Greenwich Biosciences, outside the submitted work.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
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