Annals of Pharmacotherapy
2019, Vol. 53(6) 603–611

DOI: 10.1177/1060028018822124
journals.sagepub.com/home/aop
SAGE

Cannabidiol: A New Hope for Patients With Dravet or Lennox-Gastaut Syndromes

Jeffrey W. Chen, MBA[1], Laura M. Borgelt, PharmD, FCCP, BCPS[1], and Allison B. Blackmer, PharmD, BCPS, BCPPS, FCCP[1]

Abstract

Objective: To review the efficacy, safety, pharmacology and pharmacokinetics of pure, plant-derived cannabidiol (CBD; Epidiolex) in the treatment of Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS). **Data Sources:** Relevant information was identified through EMBASE and Ovid MEDLINE (1946 to October 2018). Product labeling and https://www.clinicaltrials.gov were also reviewed. **Study Selection/Data Extraction:** English language articles evaluating efficacy and safety in humans with treatment-resistant epilepsies were reviewed; additional pharmacology and pharmacokinetic studies in humans, animals, and in vitro were also included. **Data Synthesis:** Pure, plant-based CBD is a pharmaceutical grade extract that exhibits clinically significant antiseizure properties, with a hypothesized multimodal mechanism of action. In the GWPCARE trial series, CBD displayed superior efficacy in reducing key seizure frequencies (convulsive seizures in DS; drop seizures in LGS) by 17% to 23% compared with placebo as adjunctive therapy to standard antiepileptic drugs in patients 2 years of age and older. Common adverse effects were somnolence, diarrhea, and elevated hepatic transaminases. Noteworthy drug-drug interactions included clobazam, valproates, and significant inducers/inhibitors of CYP2C19 and 3A4 enzymes. **Relevance to Patient Care and Clinical Practice:** A discussion regarding CBD dosing, administration, adverse effects, monitoring parameters, and interactions is provided to guide clinicians. CBD offers patients with DS and LGS a new treatment option for refractory seizures. **Conclusion:** This is the first cannabis-derived medication with approval from the US Food and Drug Administration. This CBD formulation significantly reduces seizures as an adjunct to standard antiepileptic therapies in patients ≥2 years old with DS and LGS and is well tolerated.

Keywords

Epidiolex, cannabidiol, CBD, GWP42003-P, epilepsy, seizure, Lennox-Gastaut, Dravet, treatment-resistant epilepsy, antiseizure medications

Introduction

Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are rare, devastating, treatment-resistant epilepsy (TRE) syndromes.[1,2] Patients experience frequent and multiple refractory seizure types despite using antiepileptic drugs (AEDs) and medical interventions such as ketogenic diets, vagal nerve stimulation, and surgery. The frequency and severity of seizures have profound impacts on quality of life, risk for injury (eg, convulsive seizures in DS, drop seizures in LGS), health care use, and increased risk for mortality.[2] Individuals with DS and LGS experience significant intellectual, behavioral, and cognitive deficits.[1,2] Clinical treatment of both DS and LGS with AEDs typically involves a trial and error approach with first-line options including valproates and clobazam for DS; valproates, lamotrigine, and topiramate are often initial choices for LGS.[1,2] A high proportion of patients experience a lack of response requiring the use of many alternative AEDs with only marginal success; treatment failure is common and

[1]University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA

Corresponding Author:
Allison B. Blackmer, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Mail Stop C238, 12850 E Montview Blvd, V20-1208, Aurora, CO 80045, USA.
Email: Allison.Blackmer@ucdenver.edu

most often a result of lack of efficacy or tolerability, leaving patients, families, and clinicians desperate for alternatives.

Cannabis-based medications derived from flowers and resin have been used as far back as ~2700 BCE for a variety of conditions, including menstrual disorders, constipation, malaria, and gout.[3] In modern medicine, English neurologists Gowers and Reynolds both referenced the use of cannabis in treating seizure disorders dating back to the late 19th century.[4,5] Nearly 100 phytocannabinoids have been identified from *Cannabis sativa* and *C indica*.[6] Δ9-Tetrahydrocannibinol (Δ9-THC) and cannabidiol (CBD) are 2 major pharmacologically active cannabinoids. Unlike Δ9-THC, CBD lacks intoxicating properties but retains potent pharmacological action, making it an attractive option for treating TREs.[3] Although federally prohibited by the Controlled Substances Act in the United States, 33 states and more than 25 other countries have legalized the production or use of cannabis for medicinal purposes.[7,8] Access to cannabis products has resulted in therapeutic advances for patients with TREs, particularly for those with DS and LGS.[9-11] However, in the United States, cannabis products are unregulated by the Food and Drug Administration (FDA), and variations in strains, potency, purity, and access exist. Furthermore, robust research regarding cannabinoids has been stifled owing to a Schedule I classification by the US Drug Enforcement Administration (DEA). To date, this has posed problems when managing patients with cannabinoids; clear information about dosing, drug interactions, efficacy, and safety are not established.

Greenwich Bioscience, a GW Pharmaceuticals LPC company, began developing a pharmaceutical-grade, liquid formulation of pure, plant-derived CBD more than a decade ago. Initial experience with this formulation for the management of TREs came from an Expanded Access Program (EAP), which evolved into a robust phase 3 clinical trial program. Making history, CBD was approved under the brand name Epidiolex in June 2018 by the FDA for the management of DS and LGS.[12] In September 2018, the DEA determined that CBD would be a Schedule V medication.[13] Additionally, the results of the Marketing Authorization Application for Epidiolex's potential approval for DS and LGS as an adjunctive treatment by the European Medicines Agency is expected in early 2019.[14] With established efficacy and safety data, CBD is now an important, unique alternative for patients with TREs. This article provides a review of the available literature and pertinent details regarding CBD to assist health care providers with use decisions.

Data Selection

Ovid MEDLINE (1946 to October 2018) and EMBASE searches using the search terms *cannabidiol, CBD, Epidiolex, GWP42003-P, epilepsy, seizure, Lennox-Gastaut, Dravet, severe myoclonic epilepsy in infancy, epilepsies, myoclonic*, and *epileptic syndromes* were conducted to identify relevant articles. The prescribing information was accessed from the product labeling, and https://www.clinicaltrials.gov identified relevant ongoing studies.

Clinical Trial Data

The foundation for the 3 pivotal trials, the GWPCARE series (Table 1[9-11]), was laid by a prospective, multicenter, open-label, EAP trial evaluating CBD in patients 1 to 30 years of age (n = 162) with TREs.[15] Included in this study were patients with more than 17 different seizure disorders/syndromes, with DS (23%) and LGS (22%) representing the 2 largest groups. Table 2[15-21] provides additional detail pertaining to this study, which preliminarily suggested CBD's positive effect in reducing seizure frequency and tolerable safety profile. Each of the 3 pivotal trials that followed was a multinational, double-blind, placebo-controlled trial with a 4-week baseline period, followed by a 14-week treatment (2 weeks of dose escalation, 12 weeks of maintenance), a 10-day taper (10% each day), and a 4-week safety follow-up period. In GWPCARE1, eligible patients must have been taking one or more AEDs and had at least 4 convulsive seizures during the 28-day baseline period. In GWPCARE4 and GWPCARE3, eligible patients must have been receiving between 1 and 4 AEDs and had a least 2 drop seizures per week during the 4-week baseline period. The primary outcome measure was percentage change in the primary seizure type (ie, convulsive seizure for DS, drop seizure for LGS), with secondary outcome measures including ≥25%, ≥50%, ≥75%, and 100% reduction in primary seizure type, reduction in total seizures, reduction in seizures other than the primary type, Caregiver Global Impression of Change Scale (CGIC), and safety outcomes.

GWPCARE1 Trial

Devinsky et al[9] evaluated adjunctive CBD (n = 61) at 20 mg/kg/d in 2 divided doses, compared to placebo (n = 59) in patients (mean 9.8 years [2.3-18.4 years]) with DS. Baseline demographics and characteristics between the groups were similar, including concomitant AEDs and medical interventions. The average numbers of concomitant AEDs were 3 ± 1 and 2.9 ± 1 in the CBD and placebo groups, respectively. The most common concomitant AEDs included clobazam, valproates, stiripentol, levetiracetam, and topiramate.

The primary outcome of monthly convulsive seizure frequency was significantly decreased in the CBD group (median = −38.9%) compared with placebo (median = −13.3%). The adjusted median difference between groups was −22.8% (95% CI = −41.1 to −5.4); $P = 0.01$. The

Table 1. Summary of Key Study Outcomes From 3 Pivotal Studies.

		GWPCARE1[9]	GWPCARE4[10]	GWPCARE3[11]
General study information	Patient population	• Dravet syndrome • n = 120 randomized, 108 completed • Ages 2-18 years (mean 9.8; range 2.3-18.4 years) • 52% Male	• Lennox-Gastaut syndrome • n = 171 randomized, 156 completed • Ages 2-55 years (mean 15.4 ± 9.2 years) • Predominantly white population	• Lennox-Gastaut syndrome • n = 225 randomized, 212 completed • Ages 2-55 years (mean ~15.5 years) • Predominantly white population
	Study arms	20 mg/kg/d (Divided into 2 doses) [n = 61] Placebo [n = 59]	20 mg/kg/d (Divided into 2 doses) [n = 86] Placebo [n = 85]	20 mg/kg/d (Divided into 2 doses) [n = 76] 10 mg/kg/d (Divided into 2 doses) [n = 73] Placebo [n = 76]
Primary outcome	Percentage change in primary seizure type[a,b]	Adjusted median difference: −22.8% (95% CI = −41.1 to −5.4; $P = 0.01$)	Estimated median difference: −17.21 (95% CI = −30.32 to −4.09; $P = 0.0135$)	Cannabidiol 20 mg/kg/d vs placebo: estimated median difference: 21.6 (95% CI = 6.7 to 34.8; $P = 0.005$) Cannabidiol 10 mg/kg/d vs placebo: estimated median difference: 19.2 (95% CI = 7.7 to 31.2; $P = 0.002$)
Secondary outcome measures during treatment period (full 14 weeks)	≥25% Reduction in primary seizure type[a,b]	OR = 2.10 (95% CI = 1.01 to 4.35; $P = 0.05$)	OR = 2.30 (95% CI = 1.24 to 4.26; $P = 0.0081$)	Cannabidiol 20 mg/kg/d vs placebo: OR = 2.11 (95% CI = 1.1 to 4.04)[c] Cannabidiol 10 mg/kg/d vs placebo: OR = 2.22 (95% CI = 1.15 to 4.28)[c]
	≥50% Reduction in primary seizure type[a,b]	OR = 2.00(95% CI = 0.93 to 4.30; $P = 0.08$)	OR = 2.57 (95% CI = 1.33 to 4.97; $P = 0.0043$)	Cannabidiol 20 mg/kg/d vs placebo: OR = 3.85 (95% CI = 1.75 to 8.47; $P < 0.001$) Cannabidiol 10 mg/kg/d vs placebo: OR = 3.27 (95% CI = 1.47 to 7.26; $P = 0.003$)
	≥75% Reduction in primary seizure type[a,b]	OR = 2.21 (95% CI = 0.82 to 5.95; $P = 0.11$)	OR = 2.75 (95% CI = 1.07 to 7.01; $P = 0.0273$)	Cannabidiol 20 mg/kg/d vs placebo: OR = 12.33 (95% CI = 2.76 to 55.13)[c] Cannabidiol 10 mg/kg/d vs placebo: OR = 4.55 (95% CI = 0.93 to 22.22)[c]
	100% Reduction in primary seizure type[a,b]	Difference 4.9 (95% CI = −0.5 to 10.3, $P = 0.08$)	N/A	N/A
	Reduction in total seizures	Difference between groups: −19.2% (95% CI = −39.25 to −1.17; $P = 0.03$)	Estimated median difference: −21.1 (95% CI = −33.3 to −9.4; $P = 0.0005$)	Cannabidiol 20 mg/kg/d vs placebo: estimated median difference in reduction 18.8 (95% CI = 4.4 to 31.8; $P = 0.009$) Cannabidiol 10 mg/kg/d vs placebo: estimated median difference in reduction 19.5 (95% CI = 7.5 to 30.4; $P = 0.002$)
	Reduction in seizure types other than primary seizure type[a,b]	NS	Estimated median difference: −26.1 (95% CI = −46.1 to −8.3; $P = 0.0044$)	Cannabidiol 20 mg/kg/d vs placebo: estimated median difference 22.4 (95% CI = 2.2 to 40.1)[c] Cannabidiol 10 mg/kg/d vs placebo: estimated median difference 28.3 (95% CI = 10.5 to 43.8)[c]
	Global impression of change	62% vs 34% Reported improved condition, $P = 0.02$	58% vs 34% Reported improved condition; OR = 2.54 (95% CI = 1.5 to 4.5; $P = 0.0012$)	Cannabidiol 20 mg/kg/d vs placebo: 57% vs 44% reported improved condition; OR = 1.83 (95% CI = 1.02 to 3.30; $P = 0.04$) Cannabidiol 10 mg/kg/d vs placebo: 66% vs 44% reported improved condition; OR = 2.57 (95% CI = 1.41 to 4.66; $P = 0.002$)
Safety	Adverse effects observed in the cannabidiol group (>10% frequency)	• Somnolence (36%) • Diarrhea (31%) • Decreased appetite (28%) • Fatigue (20%) • Vomiting (15% • Pyrexia (15%) • Lethargy (13%) • Infections (11%) • Convulsion (11%)	• Diarrhea (19%) • Somnolence (15%) • Pyrexia (13%) • Decreased appetite (13%) • Vomiting (10%)	• Cannabidiol 20 mg/kg/d • Somnolence (30%) • Decreased appetite (26%) • Diarrhea (15%) • Upper-respiratory-tract infection (13%) • Pyrexia (12%) • Vomiting (12%) • Nasopharyngitis (11%) • Cannabidiol 10 mg/kg/d: • Somnolence (21%) • Decreased appetite (16%) • Upper-respiratory-tract infection (16%) • Diarrhea (10%)
	Observed liver function test abnormalities in a subset of patients in the cannabidiol group	↑ALT ↑AST	↑ALT ↑AST ↑GGT	↑ALT ↑AST ↑GGT

Abbreviations: NS, nonsignificant; OR, odds ratio.

[a]The primary seizure type evaluated in GWPCARE1 was convulsive seizure.

[b]The primary seizure type evaluated in GWPCARE4 and GWPCARE3 was drop seizure.

[c]*P* value not reported because this was not a key secondary outcome and type 1 error was not controlled.

Table 2. Summary of Select Data Available From Open-Label, Expanded Access Program.

Citation	Study Design	Study Population	Cannabidiol dose	Study Duration	Efficacy Outcomes	Safety Outcomes	Adverse Events
Devinsky et al[15]	Prospective, multiple center, open label	Patients (age 1 to 30 years) with treatment-resistant epilepsies (n = 162 safety analysis, n = 137 efficacy analysis); mean age safety analysis: 10.5 years (0.9 to 26.2 years); mean age efficacy analysis: 10.5 years (1 to 22.2 years); 49% male	Initial 2-5 mg/kg/d, divided into 2 doses, titrated to maximum of 25-50 mg/kg/d	12 Weeks	• Median change in monthly motor seizures significantly decreased at 12 weeks: −36.5% (IQR −64.7 to 0)[a] • Post hoc analysis revealed median monthly decrease in all seizures of −34.6% (IQR = −66.7% to −9.8%) • 54 (39%) Patients had a reduction of ≥50% motor seizures • 29 (21%) Patients had a reduction of ≥70% motor seizures • 12 (9%) Patients had a reduction of ≥90% motor seizures	• Adverse events reported in 128 (78%) patients • Serious adverse events in 48 (30%) patients, including 1 death attributed to sudden unexpected death in epilepsy (unrelated to study drug)	>10% Frequency • Somnolence (25%) • Decreased appetite (19%) • Diarrhea (19%) • Fatigue (13%) • Convulsion (11%)
Szaflarski et al[16]	Prospective, multiple center, open label	Patients with treatment-resistant epilepsies (n = 607); mean age: 13.1 years (0.4 to 62.1 years); 52% male	Initial 2-10 mg/kg/d in divided doses titrated to maximum of 25-50 mg/kg/d	2 to 146 Weeks	Overall results • Decrease in median monthly convulsive seizure frequency of 51% at 12 weeks • Decrease in median monthly total seizure frequency 48% at 12 weeks[b] Convulsive seizure reduction at week 12: ≥50% Reduction in frequency: 52% ≥75% Reduction in frequency: 31% ≥100% Reduction in frequency: 11%[b] Total seizure reduction at week 12: ≥50% Reduction in frequency: 49% ≥75% Reduction in frequency: 30% ≥100% Reduction in frequency: 6%[b]	• 32 Patients (5%) withdrew from study because of adverse events • 88% Of patients experienced adverse events • 33% Experienced serious adverse events	• Diarrhea (29%) • Somnolence (22%) • Convulsion (17%) • Increase in LFTs >3× UNL (10%)
Szaflarski et al[17]	Prospective, single center, open label	Adults (n = 60) and children (n = 72) with treatment-resistant epilepsies; mean age: 19.5 ± 12.9 years; 47% male	Initial 5 mg/kg/d, titrated to a maximum of 50 mg/kg/d	48 weeks	Chalfont Seizure Severity Scale • Combined group: mean score at baseline vs 12 week: 80.7 ± 56.6 vs 39.3 ± 37.5, $P < 0.0001$ • Results also significant for pediatric group and adult group when evaluated separately[c] Seizure frequency • Pediatric patients: mean frequency at baseline versus 12 weeks: 231.8 ± 535 vs 77.6 ± 147.2, $P = 0.0112$ • Combined group (adults and pediatrics): mean frequency at baseline versus 12 weeks: 144.4 ± 407.9 vs 52.5 ± 115.1, $P = 0.0101$ • Change in seizure frequency for adults only was not statistically significant • Frequency changed between baseline and 12 weeks and remained sustained at 24 and 48 weeks of treatment	Adverse event profile • Combined group: mean score at baseline vs 12 weeks: 40.8 ± 9.5 vs 33.2 ± 9.7, $P < 0.0001$ • Results also significant for pediatric group and adult group when evaluated separately[c]	Not individually reported
Rosenberg et al[18]	Prospective, single center, open-label	Patients aged 1 to 30 years with treatment-resistant epilepsies (n = 48); median age: 11.7 years (3.1 to 27.2 years); 48% male	Initial 2-5 mg/kg/d, titrated to maximum of 50 mg/kg/d	12 Weeks	Overall quality-of-life scores: Significant improvement in mean score at baseline (37.81) vs after 12 weeks of cannabidiol (45.74), $P < 0.001$ (improvements appear distinct from effect on seizures) Median percentage change in motor seizure frequency: −39.4% (IQR = −69.6% to −12%, $P < 0.001$)	Not specifically evaluated	Not specifically reported
Gofshteyn et al[19]	Case series, multiple center, open label	Children with FIRES [n = 7 (total), n = 2 (acute), n = 5 (chronic)]; mean age at onset of SE: 7.08 years (3.92 to 8.5 years); mean timing of initiation of cannabidiol 19 to 33 days (acute phase) and 3 to 87 months (chronic phase); 5/7 male	Slow titration to maximum of 25 mg/kg/d	Acute phase observations at 4 weeks Chronic phase observations at 4 and 48 weeks	Overall outcomes: • Decreased seizure burden (eg, reduction in frequency and/or duration) in 6/7 children • Ability to wean off of AEDs (pre–cannabidiol initiation mean 7.1, post–cannabidiol initiation mean 2.8, $P = 0.002$) Acute phase outcomes (n = 2): One out of 2 patients treated had complete cessation of seizures Chronic phase outcomes (n = 5): • 90.9% ± 18.9% reduction in total seizures at 4 weeks • 65.3% ± 29.3% reduction in total seizures at 48 weeks[d]	Not specifically reported	• Dizziness (2/7) • Decreased appetite/weight loss (1/7) • Nausea/vomiting (1/7) • Tremor (4/7; likely unrelated to cannabidiol)
Hess et al[20]	Prospective, multiple center, open label	Patients with tuberous sclerosis complex (n = 18); mean age 14 years (2-31 years); 50% male	Initial: 5 mg/kg/d in 2 divided doses, titrated to maximum dose of 25-50 mg/kg/d	Primary observations at 3 months of treatment; however, data available for 12 months for some patients	Overall outcomes: • Decreased seizure frequency (median reduction in seizure frequency: 48.8%) after 3 months of treatment[e] • Responder rate after 3 months of treatment: 50% • Several patients experienced seizure freedom from specific seizure types • Response rate greater in patients concomitantly on clobazam versus those not on clobazam • 85.7% Of patients with global developmental delay experienced improvement in cognition, such as alertness, verbal communication, vocalization, cognitive availability, emotional and physical connections • Behavioral improvements observed in 66.7% of patients	Not specifically reported	>10% Frequency: • Drowsiness (44.4%) • Ataxia (27.8%) • Diarrhea (22.2%) • Agitation (16.7%) • Poor sleep (11.1%) • Irritability (11.1%)
Devinsky et al[21]	Prospective, multicenter, open label	Children and young adults with CDKL5 deficiency disorder (n = 20), Dup15q (n = 8), Aicardi (n = 19), and Doose syndrome (n = 8); 92% of patients <18 years of age; 20% male	Initial 5 mg/kg/d in divided doses, titrated to maximum dose of 25-50 mg/kg/d	48 Weeks	• Median monthly convulsive seizure frequency decreased at week 12 (51.4% reduction) and week 48 (59.1% reduction), compared with baseline • Pooled analysis of all syndromes had a combined effect that was statistically significant [$\chi^2(2) = 19.4$; $P = 0.000061$] • ≥50% Reduction in seizure frequency observed in 50% of participants at 12 weeks and 57% at 48 weeks • Post hoc analysis revealed decrease in seizure frequency between baseline and week 12 but not between weeks 12 and 48 • Treated patients were able to decrease doses of certain AEDs: clobazam, valproic acid, levetiracetam and rufinamide	• 5 Patients withdrew by week 12, 2 thought to be a result of adverse event • Overall, 4 withdrew because of adverse events	• Diarrhea (29%) • Somnolence (22%) • Fatigue (22%) • Status epilepticus (9%) • Respiratory infection (5%)

Abbreviations: AED, antiepileptic drug; FIRES, fever-induced refractory epileptic encephalopathy in school-aged children; IQR, interquartile range; LFTs, liver function tests; UNL, upper limit of normal.

[a]Variability in reductions observed for individual seizure types.

[b]Sustained reduction in seizure frequency observed over 96 weeks.

[c]Improvement in score sustained at 24- and 48-week observations but was not significantly different when compared with 12 weeks.

[d]Variable reductions observed based on specific seizure type.

[e]Variable reduction observed based on specific seizure type; greatest reduction observed in tonic-clonic seizure type.

secondary outcome measure of percentage change in total seizures (−19.2%; 95% CI = −39.25 to −1.17; $P = 0.03$) was also significant. Although not statistically significant, 43% of patients treated with CBD, compared with 27% in the placebo group (odds ratio = 2.00; 95% CI = 0.93 to 4.3; $P = 0.08$), experienced at least a 50% reduction in convulsive seizure frequency, and 3 patients in the CBD group were seizure free compared with none treated with placebo. The CGIC was significant, with 62% reporting condition improvement in the CBD group compared with 34% in the placebo group ($P = 0.02$).

In all, 93% of CBD-treated patients reported adverse events versus 75% treated with placebo; 84% of adverse events in the CBD group were mild or moderate in severity, with the most common being somnolence, fatigue, and lethargy; gastrointestinal effects; pyrexia; upper respiratory tract infection; decreased appetite; and convulsion. A majority of patients experiencing somnolence were receiving clobazam. Also, 10 patients in the CBD group underwent a dose reduction because of adverse effects, which subsequently resolved in 80% of patients. Serious adverse events were reported more commonly in the CBD group (16%) compared with placebo (5%). The serious adverse event deemed to be related to CBD—significant elevations in liver function tests (LFTs)—was observed more frequently in the CBD group, with those concomitantly on valproates more likely to have increased LFTs.

GWPCARE4 Trial

Thiele et al[10] evaluated the efficacy and safety of CBD 20 mg/kg/d in 2 divided doses (n = 86) compared with placebo (n = 85) as add-on therapy in patients (ages 2-55 years) with LGS. Baseline characteristics between the groups were similar, with a mostly white study population and a mean age of 15.4 ± 9.2 years. The median number of concomitant AEDs received during the study was 3 (range 1-5) in the CBD group and 3 (range 1-4) in the placebo group. The most commonly received concomitant AEDs included clobazam, valproates, lamotrigine, levetiracetam, and rufinamide.

The primary outcome measure of percentage change in monthly drop seizure frequency was significantly decreased in the CBD group (median = −43.9% [IQR = −69.6 to −1.9]) compared with placebo (median = −21.8% [IQR = −45.7 to 1.7]). The estimated difference between groups was −17.21% (95% CI = −30.32 to −4.09; $P = 0.0135$). CBD resulted in significant improvements in all secondary outcomes, with the exception of 100% reduction in primary seizure type. Forty-four percent of patients in the CBD group experienced a ≥50% reduction in drop seizure frequency compared with 24% in those receiving placebo (OR = 2.57; 95% CI = 1.33 to 4.97; $P = 0.0043$). Scores on the CGIC Scale were significantly improved for those receiving CBD (OR = 2.54; 95% CI = 1.5 to 4.5; $P = 0.0012$).

The total number of adverse events reported for the CBD and placebo groups were 86% and 69%, respectively. The most common adverse events included somnolence, diarrhea and vomiting, pyrexia, and decreased appetite. Concurrent use of clobazam increased the risk of somnolence in both groups. Serious adverse events were more common in the CBD group (23%) versus placebo (5%). Two serious adverse events considered to be treatment related were sleep apnea (1 patient) and increased LFTs (4 patients). Dose reduction resolved adverse events in the majority of cases. The elevations in LFTs observed occurred more frequently in patients receiving valproates.

GWPCARE3 Trial

Devinsky et al[11] evaluated 2 doses of CBD (10 mg/kg/d [n = 73] and 20 mg/kg/d [n = 76] in 2 divided doses) compared with placebo (n = 76) in patients with LGS, 2 to 55 years old. Baseline characteristics between the 3 groups were similar, with a predominantly white study population and a mean age of 15.6 years. The median number of concomitant AEDs in each group was 3 (range 1-5 in the placebo and 10 mg/kg/d group; range 0-5 in the 20 mg/kg/d group). The most common concomitant AEDs included clobazam, valproates, lamotrigine, levetiracetam, and rufinamide.

CBD at both doses resulted in significant improvements in the primary outcome measure of median percentage reduction in monthly drop seizure frequency. Patients receiving 20 mg/kg/d experienced a 41.9% decrease and those receiving 10 mg/kg/d saw a 37.2% decrease, compared with a 17.2% reduction in the placebo group. Compared with placebo, the median decrease in the 20 mg/kg/d group was −21.6% (95% CI = 6.7 to 34.8; $P = 0.005$) and in the 10 mg/kg/d group was −19.2% (95% CI = 7.7 to 31.2; $P = 0.002$). The key secondary outcome measure of ≥50% reduction in drop seizure frequency was experienced by 39% in the 20 mg/kg/d group, 36% in the 10 mg/kg/d group, and 14% in the placebo group (OR for the 20 mg/kg/d group vs placebo, 3.85 [95% CI = 1.75 to 8.47; $P < 0.001$]; OR for the 10 mg/kg/d group vs placebo, 3.27 [95% CI = 1.47 to 7.26; $P = 0.003$]). Both groups experienced a significant reduction in all seizure types compared with placebo, and CGIC scores were also significant with 57% in the 20 mg/kg/d group and 66% in the 10 mg/kg/d group, compared with 44% in the placebo group, reporting overall improvement.

Adverse events were reported in 94% of patients in the 20 mg/kg/d group compared with 84% in the 10 mg/kg/d group and 72% receiving placebo, with 89% of the adverse events being rated as mild or moderate severity. Common adverse effects were somnolence, diarrhea, upper respiratory infection, decreased appetite, pyrexia, and vomiting. Elevations in LFTs were observed in 9% of patients who received CBD, compared with zero in the

placebo group, a majority (79%) concomitantly receiving valproates. Serious adverse events were observed in 33 patients overall (13 in each CBD group versus 7 in the placebo group). Serious adverse events were deemed to be study related in 7 patients receiving CBD; reported serious adverse events included increases in LFTs, somnolence, lethargy, increased seizures during weaning (1 patient), nonconvulsive status epilepticus (1 patient), constipation, and worsening cholecystitis (1 patient).

These trials revealed CBD's efficacy in reducing the frequency of the primary seizure type over a 14-week period compared with placebo, providing compelling evidence for the role of pure, plant-derived CBD in the management of DS and LGS. CBD was associated with several adverse effects, most notably somnolence, diarrhea, elevated LFTs, and decreased appetite. These studies are strengthened by robust design, inclusion criteria, and end points applicable to practice. Yet these study data are limited by manufacturer funding and lack of specific treatment adherence measures, long-term data, qualitative outcome measures, and reported outcomes in TREs other than DS and LGS. These limitations have been preliminarily addressed in published data available from the ongoing EAP (Table 2)[15-21] and nearly 100 ongoing trials (http://www.clinicaltrials/gov). Studies reporting long-term efficacy and safety outcomes,[16,17] qualitative outcome measures,[17,18] and the role of CBD in other specific TREs[19-21] offer initial answers to these clinical questions. These studies lay a framework for robust investigations needed to further define CBD's therapeutic role.

Clinical Pharmacology and Pharmacokinetics

The anticonvulsant mechanism of action of CBD is unknown and does not appear to be related to interactions with endocannabinoid receptors; rather, a multimodal action with more than 10 potential targets identified is postulated.[3,6,22] Several targets include blockade of G-protein coupled receptor 55 (GPR55) and T-type voltage-gated calcium channels and stimulation of 5-HT_{1a} and 5-HT_{2a} receptors.[3,6]

After oral doses (5 to 20 mg/kg/d), a predictable dose response is observed.[23] CBD has an estimated bioavailability of 6%.[3] CBD is also highly lipophilic and readily crosses the blood-brain barrier. At steady state, the time to peak plasma concentration occurs between 2.5 and 5 hours, and administration with a high-fat, high-calorie meal increases the maximal plasma concentration.[22,23] CBD has a large volume of distribution, ranging from 20,963 to 42,849 L and is >94% protein bound.[22] Metabolism occurs predominantly via the liver through CYP2C19, CYP3A4, UGT1A7, UGT1A9, and UGT2B7.[22] There is one active metabolite, 7-OH-CBD, which is metabolized to the inactive metabolite, 7-COOH-CBD.[22-24] CBD is almost exclusively excreted in the feces.[22] The half-life is 56 to 61 hours.[22]

Dosage and Administration

CBD is supplied as a 100-mg/mL strawberry flavored oral solution in a sesame oil base, which will be available through a limited distribution program.[22] It is carbohydrate neutral and compatible with ketogenic diets (ie, 0 g of carbohydrate per 100 g of solution; Medical Information Team, Greenwich Biosciences, email communication, September 2018). For a more reliable treatment effect, it is recommended to administer consistently with or without a meal.[22] Specific data regarding administration via enteral feeding tubes is lacking.

Weekly titration to the minimally effective dose is recommended to assess for adverse effects that often first occur during dose escalation.[9,10,22] An initial dose of 2.5 mg/kg twice daily (5 mg/kg/d) with uptitration to 5 mg/kg twice daily (10 mg/kg/d) after 1 week is recommended. If tolerated and additional seizure control is desired, doses should be titrated in increments of 2.5 mg/kg twice daily (5 mg/kg/d) to a maximum of 10 mg/kg twice daily (20 mg/kg/d). Titration should occur no more frequently than every other day. Whereas dose adjustments are not necessary for mild hepatic impairment (Child-Pugh A), if moderate hepatic impairment (Child-Pugh B) is present, doses should be started at 1.25 mg/kg twice daily (2.5 mg/kg/d), titrating up to a maximum of 5 mg/kg twice daily (10 mg/kg/d) if greater seizure control is necessary.[22] In patients with severe hepatic impairment (Child-Pugh C), doses should be started at 0.5 mg/kg twice daily (1 mg/kg/d) and titrated to a maximum of 2 mg/kg twice daily (4 mg/kg/d). In all cases of hepatic impairment, slower uptitration is recommended. If discontinuation is warranted because of lack of efficacy or toxicity, gradual reduction is necessary to prevent the risks of increased seizure frequency or status epilepticus. Doses above what appears in product labeling have been reported in several of the EAPs, but adverse effects may be more common.[15-21]

Adverse Events, Safety, and Abuse Potential

The most common adverse events reported include gastrointestinal-related adverse effects (diarrhea, vomiting, decreased appetite/weight loss), somnolence, and increased LFTs. Although more likely to occur in patients concomitantly receiving valproates, and to a lesser extent clobazam, elevations may occur in any patient treated with CBD.[22] LFTs must be monitored at baseline and at 1, 3, and 6 months after initiation, as well as with dose changes or changes in medications known to affect LFTs. In patients

Table 3. Cannabidiol (Epidiolex), Quick Facts.

- FDA-approved indications: treatment of seizures in patients aged ≥2 years of age with Dravet syndrome or Lennox-Gastaut syndrome
- DEA Schedule: V
- Dosage form: 100 mg/mL oral solution (strawberry flavored)
- Dosing: initial 2.5 mg/kg twice daily (5 mg/kg/d), titrated at weekly intervals to minimum effective dose or 10 mg/kg twice daily (20 mg/kg/d)
- Dosage adjustment needed in hepatic impairment
- Do not abruptly discontinue
- Administration: administer consistently with or without food
- Primary drug-drug interactions: clobazam, valproates, CYP3A4 and CYP2C19 inducers and inhibitors, CNS depressants
- Common adverse events: somnolence, diarrhea, decreased appetite, elevated hepatic transaminases
- Monitoring: AST/ALT and total bilirubin at baseline and 1, 3, and 6 months after initiation and 1 month following dosing changes and/or addition of medications affecting liver function
- Product distribution: available via limited distribution (ie, specialty pharmacy)
- Manufacturer's estimated annual list price: US$32,500[34]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; DEA, US Drug Enforcement Administration; FDA, US Food and Drug Administration.

with elevated baseline transaminases, more frequent monitoring of LFTs is warranted. If hepatic transaminase levels increase to >3 times the upper limit of normal (ULN), with a concomitant increase in bilirubin of >2 ULN, or if hepatic transaminase levels are >5 times ULN alone, CBD should be discontinued.

Suicidality is a potential risk with AEDs,[25] and the package labeling includes appropriate warnings.[22] However, no suicide-related deaths or suicidal ideation (Columbia Suicide Severity Rating Scale) were reported in the pivotal trials.[9-11] Nevertheless, patients should be monitored for risk of suicidal ideation while receiving CBD.

CBD does not exert a stimulating effect on endocannabinoid receptors, explaining its minimally psychoactive or euphoric effects.[3] Indeed, in animal and human abuse potential studies, CBD did not produce rewarding effects and was deemed to have low risk for abuse and no risk for physical dependence.[22,26,27]

Drug Interactions

Coadministration with known inducers or inhibitors of CYP3A4 and CYP2C19, CBD's primary metabolic pathways, should be done cautiously.[22] In vitro data predict potential interactions with CYP1A2, CYP2B6, CYP2C8, and CYP2C9 substrates as well as UGT1A9 and UGT2B7. Concomitant administration with other central nervous system depressants may lead to increased somnolence. Furthermore, there are 2 theoretical CBD-drug transporter interactions with BCRP and ABCC1.[28,29]

Two specific drug interactions deserve repeat mention here: clobazam and valproates. CBD has been shown to elevate levels of clobazam as well as its active metabolite *N*-desmethylclobazam, which may, in part, explain observed increased somnolence.[23,30] Dose reductions of clobazam may be warranted when used concurrently. Concomitant administration with valproates increases the risk for elevations in LFTs. Interestingly, serum valproate levels do not change with coadministration, implying a pharmacodynamic rather than a pharmacokinetic interaction.[23]

Concurrent use of other AEDs (topiramate, rufinamide, zonisamide, and eslicarbazepine) have also been evaluated, with mean changes in serum levels remaining within therapeutic ranges.[31] Also, a single case report notes a potential interaction with warfarin, with warfarin dose reductions needed to maintain international normalized ratio within goal range.[32]

Relevance to Patient Care and Clinical Practice

This article provides a summary of the key clinical trial data, including the evidence from the EAP and the 3 pivotal phase III trials evaluating the effects of CBD on 2 treatment-resistant epilepsies, DS and LGS. Relevant data on dosage, administration, drug-drug interactions, adverse effects, and monitoring have been condensed into a practical guide for clinicians. The addition of CBD to the armamentarium available to patients with DS and LGS offers a new treatment option in a space where pharmacotherapy is frequently insufficient at managing multiple, refractory seizure types.

Summary

This historic FDA approval offers a unique alternative for patients with DS and LGS. Evidence from the GWPCARE trial series and the EAP as well as ongoing studies indicate CBD's efficacy in reducing seizures in these refractory and devastating epileptic disorders.[9-11,15-21,33] Although associated

with adverse events, CBD is well tolerated and is considered to be a safe and reasonable treatment option for patients 2 years of age and older with DS and LGS. The reader is referred to the Cannabidiol (Epidiolex), Quick Facts (Table 3)[34] for a snapshot view of Epidiolex. Although its exact place in therapy remains to be conclusively determined, this FDA-regulated, pharmaceutical grade cannabinoid is a new advancement and a valuable addition to the armamentarium available to treat DS and LGS.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: In the last 12 months, Dr. Borgelt received honoraria for continuing education from PharmCon, Inc and received grant support for research of CBD in pediatric epilepsy that was funded by the Colorado Department of Public Health and Environment.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Allison B. Blackmer https://orcid.org/0000-0003-3126-4204

References

1. Asadi-Pooya AA. Lennox-Gastaut syndrome: a comprehensive review. *Neurol Sci*. 2018;39:403-414. doi:10.1007/s10072-017-3188-y
2. Wirrell EC, Laux L, Donner E, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American Consensus Panel. *Pediatr Neurol*. 2017;68:18-34.e13. doi:10.1016/j.pediatrneurol.2017.01.025
3. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*. 2014;55:791-802. doi:10.1111/epi.12631
4. Gowers WR. *Epilepsy and Other Chronic Convulsive Diseases: Their Causes, Symptoms, & Treatment*. London, England: Churchill; 1881.
5. Reynolds JR. *Epilepsy: Its Symptoms, Treatment, and Relation to Other Chronic Convulsive Diseases*. London, England: Churchill; 1861.
6. Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy Behav*. 2017;70(pt B):313-318. doi:10.1016/j.yebeh.2016.11.016
7. National Conference of State Legislatures. State Medical Marijuana Laws. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. Published August 11, 2018. Accessed September 20, 2018.
8. Cannabinoid Medicines International Association for Cannabinoid Medicines. Laws and politics. http://cannabis-med.org/index.php?tpl=page&id=41&lng=en&sid=1b35fdd1438521c70b7a145c6cf33ff. Accessed December 2, 2018.
9. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med*. 2017;376:2011-2020. doi:10.1056/NEJMoa1611618
10. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2018;391:1085-1096. doi:10.1016/S0140-6736(18)30136-3
11. Devinsky O, Patel AD, Cross JH, et al; GWPCARE3 Study Group. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *N Engl J Med*. 2018;378:1888-1897. doi:10.1056/NEJMoa1714631
12. US Food and Drug Administration. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe form of epilepsy. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm611046.htm. Published June 25, 2018. Accessed September 26, 2018.
13. GW Pharmaceuticals. GW Pharmaceuticals plc and its US Subsidiary Greenwich Biosciences announce the DEA has rescheduled Epidiolex® (cannabidiol) oral solution to schedule V. http://ir.gwpharm.com/news-releases/news-release-details/gw-pharmaceuticals-plc-and-its-us-subsidiary-greenwich-0. Published September 27, 2018. Accessed December 14, 2018.
14. GW Pharmaceuticals. GW Pharmaceuticals announces the European Medicines Agency (EMA) accepts Epidiolex® (cannabidiol) marketing authorization application (MAA) for review. https://www.gwpharm.com/about/news/gw-pharmaceuticals-announces-european-medicines-agency-ema-accepts-epidiolexr. Published February 5, 2018. Accessed November 10, 2018.
15. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol*. 2016;15:270-278. doi:10.1016/S1474-4422(15)00379-8
16. Szaflarski JP, Bebin EM, Comi AM, et al. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: expanded access program results. *Epilepsia*. 2018;59:1540-1548. doi:10.1111/epi.14477
17. Szaflarski JP, Bebin EM, Cutter G, et al; UAB CBD Program. Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study. *Epilepsy Behav*. 2018;87:131-136.
18. Rosenberg EC, Louik J, Conway E, Devinsky O, Friedman D. Quality of life in childhood epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. *Epilepsia*. 2017;58:e96-e100. doi:10.1111/epi.13815
19. Gofshteyn JS, Wilfong A, Devinsky O, et al. Cannabidiol as a potential treatment for febrile infection-related epilepsy syndrome (FIRES) in the acute and chronic phases. *J Child Neurol*. 2017;32:35-40. doi:10.1177/0883073816669450
20. Hess EJ, Moody KA, Geffrey AL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. *Epilepsia*. 2016;57:1617-1624. doi:10.1111/epi.13499

21. Devinsky O, Verducci C, Thiele EA, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. *Epilepsy Behav*. 2018;86:131-137. doi:10.1016/j.yebeh.2018.05.013
22. Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc; 2018.
23. Devinsky O, Patel AD, Thiele EA, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology*. 2018;90:e1204-e1211. doi:10.1212/WNL.0000000000005254
24. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug Metab Rev*. 2014;46:86-95. doi:10.3109/03602532.2013.849268
25. US Department of Health and Human Services; Food and Drug Administartion. Statistical review and evaluation: antiepileptic drugs and suicidality. https://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm192556.pdf. Published May 23, 2008. Accessed September 20, 2018.
26. Schoedel K, Etges T, Levy-Cooperman N, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the abuse potential of purified cannabidiol (CBD) in subjects with a history of recreational polydrug use. *Neurology*. 2018;90(15, suppl):P1.266.
27. Viudez-Martínez A, García-Gutiérrez MS, Medrano-Relinque J, Navarrón CM, Navarrete F, Manzanares J. Cannabidiol does not display drug abuse potential in mice behavior. *Acta Pharmacol Sin*. 2019;40(3):358-364.
28. Holland ML, Lau DTT, Allen JD, Arnold JC. The multidrug transporter ABCG2 (BCRP) is inhibited by plant-derived cannabinoids. *Br J Pharmacol*. 2007;152:815-824. doi:10.1038/sj.bjp.0707467
29. Holland ML, Allen JD, Arnold JC. Interaction of plant cannabinoids with the multidrug transporter ABCC1 (MRP1). *Eur J Pharmacol*. 2008;591:128-131. doi:10.1016/j.ejphar.2008.06.079
30. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia*. 2015;56:1246-1251. doi:10.1111/epi.13060
31. Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP; UAB CBD Program. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia*. 2017;58:1586-1592. doi:10.1111/epi.13852
32. Grayson L, Vines B, Nichol K, Szaflarski JP; UAB CBD Program. An interaction between warfarin and cannabidiol, a case report. *Epilepsy Behav Case Rep*. 2018;9:10-11. doi:10.1016/j.ebcr.2017.10.001
33. ClinicalTrials.gov. Search results. https://clinicaltrials.gov/ct2/results?cond=Epilepsy&term=cannabidiol&cntry=&state=&city=&dist=. Accessed September 20, 2018.
34. Rubin R. The path to the first FDA-approved cannabis-derived treatment and what comes next. *JAMA*. 2018;320:1227-1229. doi:10.1001/jama.2018.11914