Treatment of Seizures Associated with Lennox-Gastaut and Dravet Syndromes: A Focus on Cannabidiol Oral Solution

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INTRODUCTION

Epileptic encephalopathies represent a group of devastating epileptic disorders that appear early in life.[1] They are characterized by pharmacoresistant generalized or focal seizures, persistent severe EEG abnormalities, and cognitive dysfunction or decline.[1] Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS) are two of the various, rare epileptic disorders classified as epileptic encephalopathies. LGS is estimated to occur in 0.1 to 0.28 people per 100,000 and is believed to account for one to four percent of all cases of childhood epilepsy.[2] LGS is one of the most severe epileptic encephalopathies of childhood-onset epilepsy. It is characterized by a triad of signs, which include multiple seizure types, slow spike-wave complexes on electroencephalographic (EEG) recordings, and impairment of cognitive function.[3]

DS is an intractable pediatric epilepsy syndrome that begins in early childhood[4] and affects an estimated 1:15,700 individuals in the U.S., or 0.0064% of the population.[5,6] It is characterized by frequent, prolonged seizures, developmental delay, speech impairment, ataxia, hypotonia, sleep disturbances, and other health problems.[6] In addition to the severe comorbid conditions associated with these diseases, DS has one of the highest rates of mortality due to sudden unexpected death in epilepsy, among other forms of childhood-onset epilepsy.[7]

Pharmacological treatment for both disorders is complex. Treatment options for patients with LGS are limited because of the resistance of seizures to pharmacological treatment.[3] Furthermore, LGS is associated with multiple seizure types that often require broad-spectrum antiepileptic drugs (AEDs) and/or polypharmacy.[8] Although a limited amount of randomized controlled trials assessing drug efficacy have been completed, felbamate, clobazam, topiramate, and lamictal have Food and Drug Administration (FDA) indications for use in LGS. Other AEDs are used for LGS in combinations that are mostly guided by anecdotal evidence and personal experience.[3] Despite the use of a wide array of AEDs, pharmacologic treatment often is not completely effective at controlling the frequent epileptic episodes.

Patients with DS often require polytherapy, as they typically experience medically refractory epilepsy.[3] First-line agents for the treatment of DS include valproate and clobazam. Although adjunctive therapies with topiramate and levetiracetam have also proved beneficial in the management of DS, complete seizure control is generally not achievable with current therapies.[9]

Cannabis has been used for centuries as a homeopathic agent. Evidence describing the effects of major plant cannabinoids, most notably cannabidiol and cannabidivarin, demonstrates consistently beneficial therapeutic effects in preclinical models of seizures, epilepsy, epileptogenesis, and neuroprotection, consistent with emerging clinical trial results.[10] Moreover, recent mounting anecdotal reports and media coverage have sparked intense interest among parents, patients, and the scientific community regarding the potential use of medical cannabis to treat seizures.[11] In response to the noted difficulties and treatment failures with current available therapies for LGS and DS, as well as increasing evidence for the use of cannabidiol (CBD) in epilepsy, the FDA approved CBD oral solution (Epidiolex®, Greenwich Biosciences, Inc.) in June 2018. CBD was approved as an additive agent for LGS and DS, making it the first plant-derived CBD pharmacologic agent approved for use in the U.S. It is the first drug available in the newest category of AEDs and is indicated for use in patients 2 years of age and older.

CLINICAL PHARMACOLOGY[12]

Mechanism of Action

The exact mechanism of CBD anticonvulsant effects is unknown in humans. CBD does not appear to interact with cannabinoid receptors to exert its anticonvulsant effects.

Pharmacodynamics

There is no relevant data on the pharmacodynamic effects of CBD.

Pharmacokinetics

Devinsky et al. conducted a study to evaluate the safety and pharmacokinetics of CBD in children with DS. Exposure to CBD and its metabolites increased in a dose-proportional fashion. The highest plasma concentrations were observed during the first two to three hours following the oral administration of CBD 5 to 20 mg/kg/day in patients.

Absorption

After oral administration of CBD, the time to maximum plasma concentration is from 2.5 to 5 hours at steady state. When co-administered with a high-fat/high-calorie meal compared to healthy individ-

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uals in the fasted state, the maximum concentration of CBD is increased fivefold, the area under the concentration curve (AUC) fourfold, and the total variability of CBD and its metabolites are reduced.

Distribution

CBD and its metabolites are > 94% protein bound *in vitro*. The volume of distribution in healthy volunteers ranges from 20,963 L to 42,849 L, indicating a high lipophilicity.

Metabolism

CBD undergoes metabolism primarily in the liver by cytochrome P450 3A4 (CYP3A4) and CYP2C19, and to a lesser extent in the gut by uridine 5'-diphosphoglucuronosyltransferase (UGT) UGT1A7, UGT1A9, and UGT2B7 isoforms to its active metabolite, 7-hydroxy-cannabidiol (7-OH-CBD). After continuous dosing, 7-OH-CBD metabolite is converted to its inactive form 7-carboxy-canabidiol (7-COOH-CBD), which has an AUC forty times higher than the parent drug. CYP3A4 and CYP2C19 are induced by several AEDs (phenytoin, topiramate, carbamazepines) and inhibited by others (e.g., valproate).

Elimination

CBD is excreted mainly in feces and to a lesser extent in urine. Based on twice-daily dosing for seven days in healthy individuals, the elimination half-life ranges from 56 to 61 hours. The clearance of CBD after a 1,500-mg dose (1.1 times the maximum recommended dosage) is 1,111 L/h.

PIVOTAL CLINICAL STUDIES

Cannabidiol in Patients With Seizures Associated With Lennox-Gastaut Syndrome (GWPCARE4): A Randomized, Double-blind, Placebo-controlled Phase 3 Trial[13]

The GWPCARE4 study was conducted to evaluate the efficacy and safety of cannabidiol compared with placebo as add-on therapy to existing AEDs for the treatment of seizures associated with LGS in patients.

The trial was conducted at 24 clinical sites in the USA, the Netherlands, and Poland, and included 171 patients with LGS aged 2 to 55 years old.

GWPCARE4 compared a dose of CBD 20 mg/kg/day (n = 86) to placebo (n = 85). The patients enrolled in the study had a diagnosis of LGS and were inadequately controlled on at least two AEDs, taking from one to four AED drugs. Patients in whom all pharmacotherapy and other interventions had been tried, including vagus nerve stimulation and ketogenic diets, were also included. Eligible patients had at least two drop seizures per week during the four-week baseline period. Patients who had clinically unstable diseases other than epilepsy, or a history of alcohol and other substance abuse including recreational cannabis and corticotrophin in the previous six months, or who had been taking felbamate for less than a year before screening were excluded. In addition, patients with a positive urine toxicology screen for tetrahydrocannabinol, and female patients who were pregnant, lactating, or planning pregnancy within three months of completing the study were excluded. The baseline period was followed by a 14-week treatment period, which included a two-week titration and 12-week maintenance period. Patients also underwent a tapering period of 10 days and a four-week safety follow-up period.

The primary endpoint was the percentage change in monthly frequency of drop seizures from baseline, measured during the 14-week treatment period. The main secondary endpoint was the proportion of patients in each treatment group to attain a 50% reduction or more in monthly frequency of drop seizures. Other secondary endpoints were the proportion of patients who achieved a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in drop seizures from baseline and percentage change in the frequency of non-drop seizures.

In the treatment group, the monthly frequency of drop seizures decreased from a median of 71.4 drop seizures per patient per month at baseline to 31.4 drop seizures—a median reduction of 43.9%. In the placebo group, the monthly frequency of drop seizures decreased from a median of 74.7 drops per patient per month at baseline to 56.3 drops—a median of 21.8%.

The secondary endpoint also showed that patients taking CBD had a significantly greater median reduction in drop-seizure frequency of 50% or more compared to those on placebo, 44% of 86 patients versus 24% of 85 patients ($P = 0.0135$), respectively. Furthermore, significantly more patients in the treatment group than in the placebo group achieved reductions of ≥ 25% or ≥ 75% in monthly frequency of drop seizures from baseline during the treatment and maintenance periods.

Cannabidiol Trial for Drug-Resistant Seizures in Dravet Syndrome[14]

The efficacy of CBD oral solution for the treatment of seizures associated with DS was evaluated in a multinational, randomized, double-blind, placebo-controlled trial in 120 patients aged 2 to 18 years old, whose seizures were not adequately controlled on current AEDs. This study compared a dose of CBD 20 mg/kg/day with placebo. Patients were eligible if they had a diagnosis of DS, were taking one or more AED, and had experienced at least four convulsive seizures while on stable AED therapy during the 28-day baseline period. All other interventions, including ketogenic diet and vagus nerve stimulation, were stable for four weeks prior to screening and remained unchanged throughout the duration of the trial. This baseline period of four weeks was followed by a two-week period of dose titration and a 12-week dose maintenance period for an overall 14-week treatment period. This was followed by a 10-day taper period, and a 4-week safety follow-up period.

The primary efficacy endpoint measured in this study was the percentage change in convulsive seizures frequency per 28 days from the four-week baseline period over the 14-week treatment period among patients who received CBD compared to placebo.

The secondary endpoint assessed the Caregiver Global Impression of Change (CGIC) score on a seven-point Likert scale of improvements (slightly improved, much improved, or very much improved) and three categories of worsening on a similar scale. Additional secondary endpoints included the number of patients who reported a reduction in convulsive seizure rate of at least 25%, 50%, 75%, or 100%; a reduction in total seizures and seizure subtypes frequency; sleep disruption, assessed on a numerical rating scale of 0 to 10, with higher scores indicating greater disruption; the Quality of Life in Childhood Epilepsy (QOLCE) questionnaire score (range, 0–100, with higher scores indicating better function); the

number of hospitalizations because of epilepsy; the number of patients with the emergence of seizure types that had not occurred during the baseline period; and the use of rescue medication.

The primary endpoint of seizure frequency was observed in the first month of the maintenance period. The median percentage reduction from baseline in the frequency of convulsive seizures was significantly greater for patients taking CBD 20 mg/kg/day than it was for patients taking placebo. A reduction in convulsive seizures decreased from 12.4 per month at baseline (range, 3.9–1,717) to 5.9 (range, 0.0–2,159) with CBD, compared with a decrease from 14.9 (range, 3.7–718) per month at baseline to 14.1 (range, 0.9–709) with placebo over the trial period. These changes represent a median of -38.9% (interquartile range, -69.5 – -4.8) for CBD versus a median change of -13.3% (interquartile range, -52.5–20.2) for placebo from baseline. The adjusted median difference in convulsive episodes between the CBD group and the placebo group was -22.8% (95% confidence interval [CI], -41.1 – -5.4; $P = 0.01$).

The secondary endpoint of a reduction in the frequency of convulsive seizures was experienced by 43% of patients in the CBD group who had at least a 50% reduction in frequency, compared to 27% of patients in the placebo group (overall response, 2.0; 95% CI, 0.93–4.30; $P = 0.08$). A monthly median decrease from 24 to 13.7 in the frequency of all seizures was observed in the CBD group, compared to a monthly median decrease from 41.5 to 31.1 in the placebo group (adjusted reduction, 28.6% vs. 9%).

Overall, 5% of patients in the CBD group became seizure-free compared to 0% of patients in the placebo group.

Rescue medication was used by 36 patients (59%) in the CBD-treatment group versus 41 patients (69%) in the control group.

On the CGIC scale, 62% of caregivers in the CBD group rated their child's overall condition as having improved, whereas only 34% of caregivers in the placebo arm rated their child's overall condition as having improved.

There was no significant difference between the groups in the sleep-disruption score, suggesting an absence of negative effect of CBD on sleep.

The QOLCE and Vineland-II scores showed no significant difference between cannabidiol and placebo.

Changes in individual seizure types and the number of patients with the emergence of seizure types that had not occurred during the baseline period were reported.[14]

SAFETY CONSIDERATIONS[12]

Drug Abuse and Dependence

CBD has not yet been assigned a schedule by the Drug Enforcement Administration under the Controlled Substances Act. In a human abuse-potential study, acute administration of cannabidiol to non-dependent adult recreational drug users at therapeutic and supratherapeutic doses in the fasted state produced responses on positive subjective measures, such as enjoyment of the drug and a willingness to take the drug again, that were within the acceptable placebo range compared to other drugs. In contrast, other drugs such as dronabinol and alprazolam produced a large increase in positive subjective measures that were greater than those produced by CBD.

In a human physical dependence study, the administration to adults of CBD 1,500 mg/day (750 mg twice daily) for 28 days did not produce any signs or symptoms of withdrawal over a six-week period following drug discontinuation. This suggests that CBD does not produce physical dependence. Overall, there were no reports of abuse-related adverse effects or physical dependence associated with this agent.

Adverse Events

The safety of CBD was evaluated in a placebo-controlled trial with a total of 323 patients with LGS or DS. In this study, the duration of treatment was up to 14 weeks. Approximately 46% of patients were female, 83% were Caucasian, and the mean age was 14 years, with a range from 2 to 48 years old. All of these patients were also on other antiepileptic drugs.

In this controlled trial, the rate of discontinuation as a result of any adverse reaction was 2.7% for patients taking CBD 10 mg/kg/day, 11.8% for those taking 20 mg/kg/day, and 1.3% for patients taking placebo. The most frequent cause of discontinuation was transaminase elevation, accounting for an incidence rate of 1.3%, 5.9%, and 0.4%, respectively.

Table 1 Most Common Adverse Effects of CBD (%)[13,14]

Organ System	CBD	Placebo
Gastrointestinal		
Diarrhea	19	6
Vomiting	9	3
Decreased Appetite	17	3
General		
Fatigue	12	2
Pyrexia	9	5
Infection		
Respiratory Tract Infection	7	5
Nervous System		
Somnolence	22	6
Lethargy	8	3
Convulsion	7	3

Of note, these patient were also taking other AEDs, including valproate.

The most common adverse events that were associated with cannabidiol included somnolence (23–25%); decreased appetite (16–22%); diarrhea (9–20%); transaminase elevations (8–16%); fatigue, malaise, and asthenia (11–12%); rash (7–13%); insomnia (5–11%); and infections (40–41%) (see Table 1). Although different adverse reactions including withdrawal, suicidal behavior, and ideation have been reported in other AEDs, these effects could not be corroborated in other studies with CBD.

Drug–Drug Interactions

Cannabidiol is metabolized by CYP3A4 and CYP2C19 isoenzymes; therefore, potential interactions may occur with drugs that are moderate or strong inhibitors and inducers of those enzymes. *In vitro* data also predict drug–drug interactions with CYP1A2, CYP2B6, UGT1A9, and UGT2B7 substrates when co-administered with CBD. Clinically significant interactions have also been reported with CYP2C8 and CYP2C9 substrates, warranting a reduction in dosage of these agents because of potential inhibition of enzyme activity by CBD.

Co-administration of CBD increases plasma concentrations of drugs that are metabolized by CYP2C19 (e.g., diazepam, clobazam) and may increase the risk of adverse reactions with these substrates.

CBD produces a threefold increase in the active metabolite of clobazam, which may increase the risk of a clobazam-related adverse reaction.

Concomitant use of CBD and valproate is associated with an increase in transaminases (alanine transaminase [ALT] and aspartate transaminase [AST]); discontinuation or reduction of CBD and/or concomitant valproate should be considered. Caution should also be taken with concomitant use of CBD and other central nervous system depressants as this may increase the risk of sedation and somnolence.

Contraindications

CBD oral solution is contraindicated in patients with a history of hypersensitivity to cannabidiol or to any other ingredients in the formulation.

Use in Specific Populations

Adequate and well-controlled studies have not been conducted with CBD in pregnant and lactating women. The administration of cannabidiol to pregnant animals produced evidence of developmental toxicity, such as increased embryo–fetal mortality in rats and decreased fetal body weights in rabbits. Other toxicities included decreased growth, delayed sexual maturation, and long-term neurobehavioral changes.

The safety and effectiveness of CBD in pediatric patients below 2 years of age have not been established. In addition, clinical trials of CBD for the treatment of LGS and DS did not include any patients older than 55 years.

CBD co-administered with other drugs is associated with increases in ALT/AST; therefore, dosage adjustments are necessary in patients with mild-to-moderate hepatic impairment and must be avoided in patients with severe hepatic impairment. Clinical trials of CBD did not include patients with renal impairment; however, CBD is mostly excreted in the feces with only minor renal clearance.

DOSAGE AND ADMINISTRATION[12]

CBD oral solution is a strawberry-flavored, clear-to-yellow solution supplied in a 105-mL amber glass bottle with a child-resistant closure containing 100 mL of oral solution (100 mg cannabidiol/mL). Two 5-mL calibrated oral-dosing syringes and a bottle adapter are packaged in a carton with CBD oral solution. The starting dosage is 2.5 mg/kg twice daily (5 mg/kg/day) and can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day) after the first week. If further reduction of seizures is needed, the dose may be increased to the maximum recommended maintenance dose of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily as tolerated.

P&T COMMITTEE CONSIDERATIONS

Although other products derived from cannabis extracts have been utilized for pain, nausea and vomiting, and anorexia, CBD oral solution is the only pharmaceutical formulation of plant-derived cannabidiol that has been adequately studied and undergone review through the FDA approval process for the treatment of two forms of childhood epilepsy. Its approval provides an additional therapy to be utilized as an add-on agent for these highly resistant forms of epilepsy. The adverse event profile of cannabidiol was favorable, with most patients tolerating the drug well despite its addition to a median of three concomitant antiepileptic drugs.[14] Additional benefits include availability of standardized dosing, pharmacokinetic data, safety and side effects information, and confidence and reliability in the procurement of the drug through regulated manufacturing companies, unlike previously used, unregulated, homeopathic cannabis-derived products. Furthermore, compared to placebo, patients experienced a significant decline in epileptic episodes.[13,14]

As part of the approval process, CBD oral solution has been rescheduled from a Schedule I agent to a Schedule V agent.[15,16] CBD oral solution is currently available to appropriate patients, and has an average wholesale price of $14.82 per 100mg/ml.[17] CBD oral solution is covered by 87% of commercial insurance plans, 94% of state Medicaid plans, and 96% of Medicare plans.[18]

CONCLUSION

CBD oral solution is a new AED class and the first plant-derived cannabidiol agent approved for two of the most severe and difficult-to-treat forms of childhood epilepsy, DS and LGS. Clinical benefits of the agent include a significant reduction from baseline in the frequency of convulsive seizures when compared to placebo.[13,14] Other benefits include available data regarding dosing, pharmacokinetics, and safety information, as well as reliability in product availability and safe manufacturing practices.

The labeling for CBD oral solution currently does not list any black box warnings. CBD is contraindicated in patients with a history of hypersensitivity to cannabidiol or to any other ingredients in CBD oral solution.[12] Other potential common adverse events include somnolence, diarrhea, fatigue, and decreased appetite.[12]

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