



## Cannabidiol Use in Refractory Epilepsy

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Cannabidiol (CBD) oral solution, Epidiolex<sup>®</sup>, was approved by the Food and Drug Administration (FDA) on June 25, 2018 for the treatment of seizures associated with Lennox Gastaut syndrome (LGS) and Dravet syndrome in patients 2 years of age and older.<sup>1,2</sup> It was given Priority Review and Fast-Track designations by the FDA, as well as orphan drug status for its potential benefit in treating refractory seizures in patients with these syndromes. The approval of CBD reflects not only the scientific evidence supporting its role as add-on therapy, but also the growing support among the families of patients with LGS and Dravet syndrome.

### Structure and Mechanism of Action

Cannabidiol is a component of the plant *Cannabis sativa* L.<sup>2-4</sup> It was isolated by Mechoulam and Shvo in 1963. Mechoulam and Carlini published the first study of its use in the treatment of refractory seizures in 1978.<sup>5,6</sup> Unlike tetrahydrocannabinol (THC), CBD has little binding affinity for cannabinoid receptors (CB<sub>1</sub> and CB<sub>2</sub>). It acts as a negative allosteric modulator of CB<sub>1</sub> and has activity at serotonin (5-HT<sub>1A</sub>), transient receptor potential cation channel subfamily V (TRPV<sub>1</sub>), and adenosine (A<sub>2A</sub>AR) receptors, in addition to acting as a positive allosteric modulator of GABA-A receptors. These mechanisms appear to produce its antiseizure, anti-anxiety, and analgesic effects.<sup>4</sup>

### Pharmacokinetics

Cannabidiol is well absorbed after oral administration, with a time to maximum concentration (T<sub>max</sub>) of 2.5 to 5 hours. Administration of CBD with a high-fat, high-calorie meal increases the maximum plasma concentrations by 5-fold and reduces variability in absorption, but adequate concentrations are achieved in both fed and fasting states. Cannabidiol is widely distributed, with > 94% protein binding. It is extensively metabolized, primarily in the liver, via cytochrome P450 (CYP) and uridine 5' diphospho-glucuronosyltransferase (UGT) enzymes CYP3A4, CYP2C19, UGT1A7, UGT1A9, and UGT2B7. The only active

metabolite, 7-OH-CBD, has an area under the concentration-time curve (AUC) 38% lower than the parent compound. Cannabidiol has an elimination half-life of 56-61 hours in adults. Patients with moderate to severe hepatic impairment (Child-Pugh classes B or C) have reduced clearance, with AUC values 2.5 to 5-fold higher than healthy adults.<sup>2-4</sup>

### Clinical Experience

The efficacy and safety of CBD was evaluated in three phase 3 randomized, double-blind, placebo-controlled trials.<sup>2</sup> Two 14-week trials were conducted in patients 2 to 55 years of age with LGS. In the first study, 171 patients were randomized to receive CBD 20 mg/kg/day or placebo. The second study enrolled 225 patients who were randomized to CBD either 10 mg/kg/day or 20 mg/kg/day or placebo. After baseline assessment, each study consisted of a 2-week dose titration followed by a 12-week maintenance period. In both, 94% of the patients were taking one or more antiseizure drugs at baseline. The most common agents, in order of frequency, were clobazam, valproate, levetiracetam, lamotrigine, and rufinamide. The primary outcome for both studies was the median percent change in frequency of atonic, tonic, or tonic-clonic seizures from baseline per 28 days. Secondary endpoints included change in total seizure frequency and change in Global Impression of Change (S/CGIC) scores.

Both studies documented a significantly greater reduction seizure frequency with CBD compared to placebo. In Study 1, the median percent change was -44 in the CBD 20 mg/kg/day group, compared to -22 in the controls (p = 0.01). In study 2, the median percent change was -37 in the CBD 10 mg/kg/day group, -42 in the CBD 20 mg/kg/day group, and -17 in the controls (p < 0.01 for both CBD groups compared to placebo). These reductions were seen within the first month of treatment and persisted throughout the 14-week treatment period. There were also significant reductions in total seizure frequency. In Study 1, the median reduction was 41% in the CBD 20

mg/kg/day group, compared to 14% in the controls ( $p < 0.01$ ). In Study 2, the median reduction was 36% in the CBD 10 mg/kg/day group, 38% in the CBD 20 mg/kg/day group, and 18% in the controls ( $p < 0.01$  for both groups). Improvement in S/CGIC scores were also greater in the patients given CBD. In Study 1, the final mean score was 3.0 in the CBD 20 mg/kg/day group, indicating slight improvement, and 3.7 in the controls, indicating no improvement ( $p < 0.01$ ). In Study 2, S/CGIC scores were 3.0, 3.2, and 3.6 in the CBD 10 mg/kg/day, CBD 20 mg/kg/day, and placebo groups, respectively ( $p < 0.01$  and  $p=0.04$ ). In Study 1, three patients (4%) in the CBD 20 mg/kg/day group became seizure-free, while in Study 2, three of the 73 patients (4%) in the CBD 10 mg/kg/day group, five of the 76 patients (7%) in the CBD 20 mg/kg/day group, and one of the 76 controls became seizure-free.

The third premarketing study evaluated the effectiveness of CBD in 120 children and adolescents with Dravet syndrome.<sup>2</sup> All patients had continued seizures while receiving one or more antiseizure medication, vagal nerve stimulation, or a ketogenic diet. They were randomized to either CBD 20 mg/kg/day or placebo, with assessment, titration, and maintenance phases similar to the first two studies. The primary outcome was median percent change in convulsive seizures from baseline per 28 days. As in the LGS studies, there was a significant improvement in the CBD group as early as 4 weeks after starting treatment which continued throughout the study, with a median change of -39 compared to -13 for the controls ( $p = 0.01$ ). Four of the 60 patients in the CBD group (6.7%) were seizure-free during the maintenance period; none of the controls were seizure-free.

In a new paper in *Epilepsy & Behavior*, Szaflarski and colleagues from the University of Alabama published a single-center prospective open-label study describing their early experience as one of several CBD expanded access programs in the United States.<sup>7</sup> A total of 72 children (mean age  $10 \pm 5$  years) and 60 adults with refractory seizures were included in the analysis. Treatment was initiated with a dose of 5 mg/kg/day and titrated to a maximum of 50 mg/kg/day. Patients were assessed at 12, 24, and 48 weeks. Most patients (77%) continued treatment after the last evaluation. Mean Chalfont Seizure Severity Scale (CSSS) scores decreased from 80.7 to 39.2 at 12 weeks ( $p < 0.0001$ ) and remained stable thereafter. Seizure frequency per 14 days declined from a mean of 144.4 at baseline to 52.2 days at 12 weeks ( $p = 0.01$ ) and remained stable. While most patients experienced benefit, 23 (17%) discontinued treatment due to lack of efficacy. Adverse effects declined throughout the study, likely the result of both acclimation to the sedative effects of CBD and the reduction in the doses of valproate and clobazam necessitated by the introduction of CBD.

The investigators from the University of Alabama CBD program also recently published a case series of three patients treated for seizures associated with brain tumors.<sup>8</sup> The patients, 40, 30, and 17 years of age, who had refractory seizures associated with ganglioglioma (in the first two cases) and an oligodendroglioma were treated and assessed as in the previous paper. Mean seizure frequency decreased by 58%, 94%, and 21% in the three patients, respectively. All had improvement in CSSS scores.

Two other papers representing cumulative data from multiple expanded access sites add further evidence of the utility CBD in refractory seizures. Devinsky and colleagues described 55 patients with seizures associated with genetic mutations, including CDKL5 deficiency disorder, Aicardi syndrome, Dup15q syndrome, and Doose syndrome who were treated with CBD between 2014 and 2016.<sup>9</sup> The median percent change in convulsive seizure frequency from baseline was 51.4% at week 12 (IQR 9-85%) and 59.1% at week 48 (IQR 14-86%). An additional report from Gofshteyn and colleagues described the use of CBD for seven children with febrile infection-related epilepsy syndrome (FIRES).<sup>10</sup> All patients had refractory seizures despite other antiseizure drugs, immunotherapy, vagal nerve stimulation, or the ketogenic diet. Six patients showed improvement in both seizure frequency and duration after starting CBD. One patient expired during treatment. Of those surviving until the end of the study, one showed no improvement, but five became ambulatory, including one was able to walk with assistance. Four regained the ability to speak. Initiation of CBD also allowed the weaning of other antiseizure drugs, with a mean reduction of four drugs per patient.

#### Contraindications and Warnings

Use of CBD oral solution is contraindicated in patients with a history of hypersensitivity to any component of the product, including sesame seed oil. In clinical trials, one patient receiving CBD developed erythema, pruritus, and angioedema.<sup>2</sup>

Hepatic injury was observed with CBD in clinical trials.<sup>2</sup> Most cases were mild elevations in serum transaminases, but rare cases of severe hepatotoxicity have been reported. In premarketing studies, the incidence of alanine aminotransferase (ALT) levels 3 times greater than the upper limit of normal (ULN) was 13% in patients receiving CBD versus 1% in patients given a placebo. Elevations in transaminases appear most often within the first 2 months of treatment, but have been reported as long as 18 months after initiation of therapy. Resolution during continued treatment occurred in one-third of patients, with the others resolving after dose reduction or removal. Discontinuation was necessary in 2.7% of the patients taking 10 mg/kg/day and in 11.8% of those taking 20 mg/kg/day, compared to 1.3% in the controls.

Serum transaminases and a total bilirubin level should be obtained prior to starting treatment, at 1, 3, and 6 months, and periodically thereafter. Levels should also be evaluated within 1 month of any dosage change or with the addition of any medication known to interact with CBD. Treatment with CBD should be stopped in patients with transaminases 3 times greater than the ULN or a bilirubin level greater than 2 times the ULN. Restarting therapy may be considered in patients with transaminase elevation less than 5 times the ULN. Families should be aware of the need to report any signs of significant nausea, vomiting, abdominal pain, loss of appetite, jaundice, or dark urine to a health care provider.

As with other antiepileptic drugs, the prescribing information for CBD includes a warning regarding an increased risk for suicidal ideation, suicide attempts, new or worsening depression, agitation, aggression, oppositional behaviors, anxiety, and panic attacks.<sup>2</sup> Families should be aware of the need to immediately contact a healthcare provider for any unusual changes in mood or behavior, signs of depression, suicidal thoughts or behavior, or self-harm.

Cannabidiol was previously categorized as a Schedule I substance by the United States Drug Enforcement Agency (DEA). It was recategorized as a Schedule V controlled substance on August 27, 2018.<sup>2,11</sup> This change was based in part on a study comparing the abuse potential of CBD with alprazolam or dronabinol.<sup>12</sup> Forty-three adult recreational polydrug users volunteered to complete this single-dose, randomized, double-blind, placebo and comparator-controlled trial. While alprazolam (2 mg) and dronabinol (10 mg and 30 mg) produced significantly higher scores on the Drug-Liking, Overall Liking, and Take Drug Again visual analog scales than placebo ( $p < 0.0001$ ), scores following a 750 mg CBD dose were no different than placebo ( $p = 0.51$ ). Doses of 1,500 mg and 4,500 mg, produced higher scores, but were still much lower than the other drugs. Unlike alprazolam and dronabinol, there were no observable effects of CBD on cognitive and psychomotor tests.

#### Adverse Effects

The adverse effect profile of CBD was compiled from data in 689 children and adults with LGS or Dravet syndrome enrolled in clinical trials and in 161 patients treated under expanded access or compassionate use programs.<sup>2</sup> Somnolence, sedation, and lethargy were the most commonly reported adverse effects in the three premarketing trials, occurring in 32% of treated patients and 11% of the controls. Symptoms were more frequent in patients taking higher CBD doses: 27% in patients taking 10 mg/kg/day, compared to 34% in those taking 20 mg/kg/day. Other adverse effects occurring in 5% or more of patients included decreased appetite (in 16% of patients receiving CBD, compared to 5% of

patients in the placebo group), diarrhea (9% versus 9%), fatigue, malaise, and asthenia (11% versus 4%), rash (7% versus 3%), insomnia or sleep disorders (11% versus 5%), and infections (41% versus 31%). Weight loss of more than 5% occurred in 16% of patients given CBD during the controlled premarketing trials, compared to 8% of the patients given placebo. This decrease was found to be dose-related, occurring in 18% of patients receiving a CBD dose of 20 mg/kg/day, but only 9% of those taking 10 mg/kg/day. Decreases in hemoglobin and hematocrit were reported in 30% of patients taking CBD versus 13% of controls. A reversible 10% increase in serum creatinine has also been reported in adults with LGS or Dravet syndrome within the first two weeks of starting therapy with CBD.<sup>2</sup>

#### Drug Interactions

Cannabidiol is a potent inhibitor of several enzymes, including CYP2C19. Concomitant administration of CBD with clobazam, a substrate for CYP2C19, has been shown to produce up to a 3-fold increase in the concentration of the active N-desmethyloclobazam (norclobazam) metabolite, increasing the incidence of somnolence, sedation, and lethargy. In premarketing studies, these adverse effects were reported in 46% of patients taking clobazam with CBD, compared to 16% of patients taking CBD alone.<sup>2</sup> Similar findings were reported in an open-label safety study conducted by Gaston and colleagues at the University of Alabama CBD program.<sup>13</sup> These authors, as well as others, have suggested reducing the clobazam dose when starting CBD, although specific recommendations have not been determined.

Cannabidiol is also a strong inhibitor of CYP2C8 and CYP2C9, which may result in increased concentrations of drugs such as phenytoin, topiramate, and rufinamide. It also inhibits UGT1A9, increasing concentrations of diflunisal, fenofibrate, and propofol, as well as UGT2B7, increasing concentrations of gemfibrozil, lamotrigine, lorazepam, and morphine. Either inhibition or induction may occur with CBD use in patients taking drugs metabolized by CYP1A2 such as caffeine, theophylline, and zonisamide, as well as those metabolized by CYP2B6, such as bupropion and efavirenz. The effect of CBD on these medications is difficult to predict.<sup>2,13</sup>

The risk for hepatotoxicity is higher with concomitant use of CBD and clobazam or valproate. Elevations in ALT greater than 3 times the ULN occurred in 30% of patients taking CBD with both valproate and clobazam, 21% of those taking CBD with valproate, 4% in those taking CBD with clobazam, and 3% with CBD alone.<sup>2</sup> A significant increase in serum transaminases with concomitant CBD and valproate use was also reported by the UAB CBD program.<sup>13</sup> The mean ALT level in the CBD/valproate group was 35.3 U/L compared to 23.7 U/L in those not taking valproate ( $p = 0.026$ ). Mean AST values were

37.1 U/L and 23.9 U/L in the two groups, respectively ( $p = 0.003$ ). In both groups, the mean values were within the normal range.

Administration of moderate or strong CYP3A4 or CYP2C19 inhibitors will increase plasma CBD concentrations, resulting in a greater risk for adverse effects. Conversely, agents that are moderate or strong CYP3A4 or CYP2C19 inducers will decrease CBD concentrations and may reduce efficacy. Dosage adjustment should be considered when using these combinations. Use of CBD with opioids or other central nervous system depressants may result in excessive sedation and the need for close monitoring.

#### Availability

Cannabidiol is available as a 100 mg/mL strawberry-flavored oral solution.<sup>2</sup> The oil-based solution is clear, ranging in color from colorless to yellow. It should be stored at room temperature and not refrigerated or frozen. Any CBD solution remaining in the bottle 12 weeks after it was first opened should be discarded. Each bottle of CBD is packaged with an adapter for use with a calibrated oral syringe to ensure accuracy of the dose given. Two 5 mL syringes are included in the package. A 1 mL oral syringe may be obtained through the pharmacy for smaller doses.

#### Dosing Recommendations

The recommended dose for CBD initiation is 2.5 mg/kg given orally twice daily (5 mg/kg/day).<sup>2</sup> After one week, the dose can be increased to the typical maintenance dose of 10 mg/kg/day. In patients not responding to 10 mg/kg/day, the dose may be increased weekly by increments of 2.5 mg/kg/day to a maximum of 20 mg/kg/day. If a more rapid escalation is necessary, the titration from 10 mg/kg/day to 20 mg/kg/day may be made with by increasing the dose every other day. Doses should be given at consistent times, with or without food. If discontinuation of CBD is necessary, it should be done gradually over several weeks to minimize the risk for increased seizure frequency or status epilepticus.

Cannabidiol doses should be reduced in patients with moderate or severe hepatic impairment (Child-Pugh classes B or C).<sup>2</sup> In moderate impairment, the manufacturer recommends an initial dose of 1.25 mg/kg twice daily, with a maximum dose of 5 mg/kg twice daily. Patients with severe hepatic impairment should begin therapy with a dose of 0.5 mg/kg twice daily, increasing to a maximum dose of 2 mg/kg twice daily. Dose titration may also be slowed from weekly to every two weeks to allow a greater period for assessment before dose escalation.

#### Summary

The FDA approval of CBD oral solution provides another new option for the treatment of refractory seizures in children and adults with LGS and Dravet syndrome. Early research suggests that

CBD may also be of value in patients with refractory seizures associated with brain tumors, genetic syndromes, or FIRES. While CBD is generally well tolerated, patients should be closely monitored for adverse effects, including hepatotoxicity, and any new medications should be evaluated for potential interactions with CBD prior to initiation.

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