

Cannabidiol in epilepsy: The indications and beyond

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Abstract

Epilepsy, although common, remains difficult to treat with as much as 30% of patients having treatment-resistant conditions. Lennox-Gastaut syndrome and Dravet syndrome are childhood-onset epilepsies and among the most difficult to treat. Cannabidiol has been approved by the Food and Drug Administration to treat these conditions in individuals over 2 years of age; however, there is a great deal of interest in off-label use. This article examines 3 cases: 1 of a patient with Lennox-Gastaut syndrome, 1 of off-label use of cannabidiol to treat epilepsy, and 1 of nonprescription forms of cannabidiol to treat epilepsy.

Keywords: epilepsy, treatment-resistant epilepsy, cannabidiol, cannabinoids, Lennox-Gastaut syndrome, Dravet syndrome

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Introduction

Epilepsy is 1 of the most common neurological disorders, occurring in about 1% of the population.¹ However, about 30% of individuals with epilepsy continue to have seizures even with medication therapy.² In 1 study,² only 47% of patients responded to the first antiepileptic drug (AED) given, and an additional 13% responded to the second medication tried as monotherapy. These patients who did not respond to a first, second, or third AED are termed treatment resistant, refractory, or intractable.² Given these data, having more AEDs may help treat patients with refractory epilepsy.

In June 2018, cannabidiol (CBD) was approved by the US Food and Drug Administration (FDA) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.³ Both before and after this approval, there has been a flurry of interest in use of the prescription CBD product (CBD-Rx; Epidiolex®, Greenwich Bioscience, Inc, Bethesda, MD), both on- and off-label, and using CBD available from other nonprescription sources for treatment of epilepsy. Although there are approximately 100 cannabinoids in the plant *Cannabis sativa*, the main ones with possible antiepileptic effects are Δ^9 -tetrahydrocannabinol (THC), Δ^9 -tetrahydrocannabivarin, cannabidivarin, Δ^8 -tetrahydrocannabinol, cannabinol, and CBD.⁴ There are a number of pharmaceutical and nonpharmaceutical products that contain CBD and/or THC (Table 1).

Cannabinoids bind to G-protein-coupled cell membrane cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors as well as G protein-coupled receptors (GPRs) 18, 55, and 119; transient receptor potential vanilloid type 1 channel (TRPV1), and peroxisome proliferator-activated receptor γ .⁹ The CB1 receptors are found throughout the central nervous system and concentrate in the cortex, basal ganglia, hippocampus, and cerebellum on axon terminals and preterminal axon segments. And the CB2 receptors are less abundant and are found on microglia, vascular tissues, immune cells, and a few neuron types.¹⁰



TABLE 1: Cannabinoid formulations^{3,5-8}

| Product | Formulations | THC Content (Dry Weight), % | CBD Content (Dry Weight), % |
|-------------|---------------------------------------------|-----------------------------|-----------------------------|
| Cannabis | Leaves and flowers for smoking ^a | 0.3 to 80 | 20 to 99.7 |
| | Oils ^a | | |
| | Edible products ^a | | |
| | Dronabinol oral capsules (Marinol®) | 100 | 0 |
| | Dronabinol oral solution (Syndros®) | | |
| Cannabidiol | Oral solution (Epidiolex®) | 0 | 100 |
| | Oils (and many others) ^a | <0.3 | >99.7 |
| Hemp seed | Oils ^a | 0 | 0 to trace |
| Nabiximols | Oral mucosal spray (Sativex®) ^a | 50 | 50 |

CBD = cannabidiol; THC = Δ^9 -tetrahydrocannabinol.

^aNot approved by the US Food and Drug Administration.

Cannabinoid type 1 receptor activation causes decreased presynaptic glutamate release.⁹

Endogenous cannabinoids (endocannabinoids) seem to decrease excitotoxicity by occupation of the CB₁ receptors on glutamatergic neurons. Two prevalent endocannabinoids are anandamide and 2-arachidonoylglycerol.¹¹ There is some support that the endocannabinoid system is involved in epilepsy; a small study of 12 patients with newly diagnosed temporal lobe epilepsy who had not yet been treated was conducted.¹² Cerebrospinal fluid was collected from the 12 patients and 12 normal controls and analyzed for anandamide. The amount of the anandamide was reduced in patients with epilepsy compared to control subjects.¹² Another study¹¹ compared brain tissue samples from people with and without epilepsy. In subjects with epilepsy, CB₁ receptor mRNA was downregulated to about one-third of the amount in those without epilepsy. The CB₁ receptors were also decreased in the hippocampus, particularly the dentate gyrus in patients with epilepsy. The amounts of 2-arachidonoylglycerol were also decreased in sclerotic hippocampal tissues in patients with epilepsy.¹¹ Taken together, these studies show decreased endocannabinoid involvement in people with epilepsy. The endocannabinoid system also appears to be involved with decreasing neuroinflammation.¹⁰ Both 2-arachidonoylglycerol and anandamide contribute to the body's synthesis of arachidonic acid, and cyclo-oxygenase-2 (COX-2); brain concentrations are increased in people with epilepsy, suggesting neuroinflammation may contribute to epilepsy.¹⁰

THC is 1 of the psychoactive components in *C. sativa*, and it binds to CB₁ and CB₂ receptors.¹³ CBD is non-psychoactive. At pharmacological concentrations resulting from 25 mg/kg/d dosing, CBD has low affinity for CB₁ or CB₂ receptors although it may act as an inverse agonist for the CB₁ receptor.¹³ CBD may also block the breakdown of anandamide.⁴ CBD has been hypothesized to work by 3

mechanisms: antagonizing GPR55, desensitizing the TRPV₁ channels, and inhibiting the equilibrative nucleoside transporter 1 adenosine reuptake pumps.⁴ The first mechanism, antagonizing the GPR55 receptor, reduces calcium release from intracellular calcium stores and decreases calcium concentrations.¹⁴ The second mechanism, desensitizing the TRPV₁ channels, reduces entry of calcium into the cell and also decreases calcium concentrations.^{4,15} The third mechanism, inhibiting equilibrative nucleoside transporter 1 adenosine reuptake pumps, reduces neuronal hyperexcitability.⁴ The net effect of these potential mechanisms is decreasing intracellular calcium and decreasing intracellular adenosine, which reduces neuroexcitability and neurotransmitter vesicular release and potentially modulates neuroinflammation.^{14,16} Reduced neuroexcitability and vesicular release decrease neurotransmission between neurons and, ultimately, seizure activity. At high doses, CBD may have neuroprotective effects. Its administration reduced atrophy and death of interneurons after status epilepticus in rats.⁴ CBD and THC inhibit COX-2 activity.¹⁰ CBD also decreases the activity and metabolism of 5-lipoxygenase in cell cultures.¹⁰ The decrease in COX-2 and 5-lipoxygenase activity lead to decreased inflammation in the brain. With multiple potential mechanisms of action, CBD may be a helpful

Take Home Points:

1. A prescription cannabidiol product offers a new therapeutic option for patients with Lennox-Gastaut syndrome and Dravet syndrome.
2. There is scant evidence for off-label use of cannabidiol at this time although trials are ongoing.
3. Nonprescription cannabidiol products and medical marijuana have purity and variability concerns, and their use cannot be condoned at this time.

TABLE 2: Common adverse effects of cannabidiol^{3,17,22,23}

| Adverse Effect | Frequency, % |
|------------------------------|--------------|
| Infections | 40 to 41 |
| Somnolence/sedation | 23 to 32 |
| Decreased appetite | 16 to 22 |
| Fatigue | 11 to 12 |
| Diarrhea | 9 to 20 |
| Liver transaminase elevation | 8 to 16 |
| Rash | 7 to 13 |
| Agitation | 5 to 9 |

addition to the AED armamentarium. The remainder of the article presents patient cases to illustrate labeled and off-label indications for CBD-Rx as well as use of nonprescription CBD products.

Cannabidiol to Treat DS or LGS

A 16-kg 4-year-old with LGS and developmental delay presented to the clinic for medication adjustments to reduce focal and atonic seizures. Current medications were lamotrigine, rufinamide, and clobazam. Previous medications included valproic acid, topiramate, felbamate, and lacosamide. Currently, the patient experienced 60 to 70 seizures/wk, 10 of which are atonic. Past medical history included intracranial hemorrhage at birth.

LGS is a severe form of epileptic encephalopathy.¹⁷ The incidence is about 2 cases per 100 000 people per year with a prevalence of 0.26 per 1000 people.¹⁸ However, it makes up 2% to 5% of childhood epilepsies.¹⁸ Patients typically present at 1 to 8 years of age, and seizures usually continue into the adult years.¹⁹ Patients often have multiple seizure types, which are usually treatment resistant. There is a high rate of drop seizures in LGS. Drop seizures can refer to either an increase in motor tone (tonic seizure) or a loss of motor tone (atonic seizure), which causes the patient to fall and puts the patient at risk of injury. Cognitive dysfunction is common in LGS.²⁰ Due to the treatment-resistant nature of LGS and drop attacks, patients with LGS are at a 14-fold risk of dying compared to the general population.²¹

Two double-blind, placebo-controlled studies^{18,22} have used CBD-Rx to treat patients with treatment-resistant LGS. In both studies, participants had a mean of 6 prior AEDs and were concurrently using a mean of 3 AEDs. The first study (GWPCARE3) was a 14-week study of CBD-Rx 10 mg/kg/d, 20 mg/kg/d, or placebo, enrolling 225 patients with LGS. The mean age was 15 to 16 years with a range of 2.5 to 48 years; 30% of patients were older than 18 years. At baseline, patients had a median number of seizures of 180.6 (placebo group), 165 (10 mg/kg/d group),

and 174.3 (20 mg/kg/d group) over 28 days. Of these, 80.3 (44.5%), 86.9 (52.7%), and 85.5 (49.1%) were drop seizures, respectively. After treatment, subjects had reduced drop seizures by 37.2% (CBD-Rx 10 mg/kg/d) or 41.9% (CBD-Rx 20 mg/kg/d) versus 17% (placebo) per 28 days ($P=.002$ for 10 mg/kg/d vs placebo; $P=.005$ for 20 mg/kg/d vs placebo). Four percent of the 10 mg/kg/d group and 7% of the 20 mg/kg/d group became seizure free once a maintenance dose was reached compared to 1% of the placebo group. Adverse effects were common with 94% of the CBD-Rx 20 mg/kg/d group reporting mostly mild-to-moderate adverse events compared to 72% of the placebo group.¹⁷ Table 2 lists common adverse effects of CBD-Rx.

The second study (GWPCARE4) enrolled 171 patients with treatment-resistant LGS. Patients received 20 mg/kg/d CBD-Rx or placebo for 14 weeks. The median reduction in drop seizure frequency was 43.9% compared to 21.8% in the placebo group (difference of -17.21 , $P=.0135$). Adverse events were common, occurring in 86% of the CBD-Rx group and 69% in the placebo group.²² An open-label extension to these 2 studies^{18,22} followed 299 patients for a mean of 38 weeks with 208 patients completing 48 weeks of treatment.²⁴ Unlike the 2 placebo-controlled studies, the dose in this open-label trial could be adjusted up or down by the treating clinician. The mean dose was 22.8 mg/kg/d. Median drop seizures were reduced by 48.2% compared to baseline with no loss of efficacy during the follow-up. Adverse effects, mostly mild to moderate, were reported in 92.1% of patients; however, 25.7% of patients had serious adverse effects, including status epilepticus (7.1%), convulsion (5.5%), pneumonia (2.5%), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increase (1.6%), or pneumonia aspiration (1.6%).²⁴ The FDA-approved indication for CBD-Rx is treatment of seizures associated with LGS or DS in patients 2 years of age and older.³ The maximum maintenance dose of CBD-Rx is 20 mg/kg/d.³

The studies of CBD-Rx in LGS demonstrate significant improvement in number of seizures, particularly drop attacks, in patients. However, they are unlikely to become seizure-free. Based on the results of these studies, the patient is a good candidate for CBD-Rx therapy. The patient's epilepsy is treatment resistant despite treatment with agents that have efficacy data in LGS. The patient experiences several drop seizures weekly, increasing the risk of injury. The patient has had therapeutic trials of many agents with limited efficacy, and CBD-Rx presents a new option with good clinical trial-based evidence to support its use. The CBD-Rx can be added directly to the regimen with alterations in other medications if adverse effects, such as sedation, are bothersome. If the CBD-Rx proves effective, the patient's medication regimen could

TABLE 3: Pharmacokinetic parameters of cannabidiol in fasting and fed states³⁰

| Pharmacokinetic Parameter | Value | |
|---------------------------------|---------------------|---------------------|
| | Fasting | Fed |
| Maximum concentration in plasma | 0.039 ng/mL | 0.45 ng/mL |
| Volume of distribution | 1515 L/kg | 194 L/kg |
| Area under the curve | 0.53 ([h×ng]/mL)/mg | 2.57 ([h×ng]/mL)/mg |
| Half-life | 38.9 h | 24.3 h |
| Clearance | 1887 L/h | 388 L/h |

then be streamlined by tapering 1 or more of the other medications.

The other form of epilepsy for which CBD-Rx has FDA approval is DS. DS is a rare (prevalence of 0.025 to 0.05 cases per 1000 individuals) form of epileptic encephalopathy.²⁵ Children who are eventually diagnosed with DS usually present in the first year of life with status epilepticus, and then, other seizure types (focal, absence, myoclonic) develop. The patients have cognitive dysfunction, and intellectual disabilities develop. Standard AEDs, such as topiramate, levetiracetam, and valproate, are often ineffective. The mortality rate is high (15.84/1000 person-years) with the median age of death being 7 years old.²⁶

Two randomized, double-blind, placebo-controlled studies,^{23,27} GWPCARE1 and GWPCARE2, have been conducted in patients with DS. GWPCARE1 compared CBD-Rx 20 mg/kg/d versus placebo in 120 patients with DS.²³ At baseline, patients had 12 to 14 seizures/28 days. In the CBD-Rx group, a mean seizure decrease of 38.9% (12.4 seizures/mo at baseline to 5.9 seizures/mo) was seen. In the placebo group, the change was 13.3% (14.9/28 days to 14.1/month). The median difference between the CBD-Rx and placebo groups was statistically significant ($P=.01$).²³ GWPCARE2 randomized 199 patients with DS to placebo, CBD-Rx 10 mg/kg/d, or CBD-Rx 20 mg/kg/d for 14 weeks. The main outcome measure was the percentage reduction in convulsive seizures compared to a 4-week baseline frequency. Convulsive seizures were reduced 26.9% for the placebo group, 48.7% for the CBD-Rx 10 mg/kg/d group, and 45.7% for the CBD-Rx 20 mg/kg/d group. Both the 10 and 20 mg/kg/d groups had statistically significantly fewer convulsive seizures compared to the placebo group ($P=.01$ and $P=.03$, respectively).²⁷ A long-term, open-label, follow-on study²⁸ of 264 patients with DS who had participated in previous trials was conducted. Mean treatment duration was 274 days, and the mean dose was 21 mg/kg/d, which is higher than the currently maximum recommended dose. The efficacy benefits were sustained

with similar adverse effects. However, 17.2% of patients, all of whom were taking concomitant valproic acid, developed liver transaminase elevations ≥ 3 times the upper limit of normal.²⁸ Liver enzyme increases were also seen with the CBD-Rx and valproic acid combination in another observational study.²⁹ The recommendation for monitoring liver enzymes in all patients taking CBD-Rx, with or without valproic acid, is for ALT, AST, and bilirubin to be obtained at baseline; 1, 3, and 6 months; and then periodically with more frequent monitoring if dose increases are needed.³ If patients have AST or ALT greater than 3 times the upper limit of normal with a bilirubin 2 times the upper limit of normal, the manufacturer recommends discontinuation of CBD-Rx.³ Because valproic acid is a mainstay of DS therapy, particular attention should be paid to liver function monitoring. The above trials demonstrate significant improvement in seizure frequency for patients with DS; however, patients are unlikely to become seizure-free.

The initial dose of CBD-Rx is 2.5 mg/kg twice daily for 1 week, then increasing to 5 mg/kg twice daily. Further increases can be made as needed and tolerated to a maximum of 10 mg/kg twice daily.³ Dose adjustments are necessary for moderate or severe hepatic disease.³ For the patient case, the recommended dose is 40 mg twice daily, increasing to 80 mg twice daily after 1 week. The dosage form is a 100-mg/mL strawberry-flavored oral solution and is administered as 0.4 mL for the first week, then 0.8 mL afterward. Patients should be given a calibrated dosing device to assure accurate measurement. A 5-mL calibrated oral syringe is provided with product packaging, but often, patients need a 1-mL device.³ There are significant differences in pharmacokinetic parameters when the dose is given with food. Eight subjects with intractable epilepsy were compared after eating a high-fat meal and after fasting (Table 3).³⁰ Record-keeping of seizures during this study was poor, but 1 patient noted a decrease from an average of 7 seizures daily in a fasting state to 1 seizure/d in a fed state. No differences in cognition were noted between the fasting and fed conditions.³⁰ Thus, patient's caregivers should try to achieve consistency with dosing regarding meals. Because of the potential of CBD-Rx to cause nausea and vomiting, dosing with food may be preferred.

CBD is heavily metabolized by the cytochrome (CYP) P450 system, specifically by CYP2C19 and CYP3A4.³ Therefore, drug-drug interactions are a concern. Moderate-to-strong inducers of CYP3A4 or CYP2C19 decrease CBD concentrations, and moderate-to-strong inhibitors increase CBD concentrations. CBD inhibits UGT1A9, UGT2B7, CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C11, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP3A7, and CYP3A17.³¹ CYP2C19 is particularly important for patients with epilepsy because clobazam, diazepam,

phenytoin, and valproic acid are metabolized via this pathway.³ Several investigations of the interaction between CBD and clobazam have been undertaken because of the common use of clobazam in patients with LGS, DS, and other treatment-refractory epilepsies. Clobazam has an active metabolite *N*-desmethylclobazam, which is itself metabolized by CYP2C19.²⁹ If the desmethylclobazam concentration is increased because of this interaction, one could expect a decrease in seizures and/or an increase in adverse effects with the combination. In a 2016 study³² of CBD-Rx in patients with treatment-resistant epilepsy (mean 3 AEDs), 51% of patients receiving clobazam had a 50% reduction in motor seizures compared to 27% of patients who were not receiving clobazam. To further explore this interaction, a clinical trial simulation was conducted.³³ In this simulation, the investigators compared the drop seizure frequency reduction between simulated patients who had been given CBD-Rx and clobazam to those who were only given CBD-Rx. The patients were based on those in the GWPCARE3 trial.¹⁷ The results suggest a 4-fold increase in clobazam serum concentrations could be caused by the interaction between clobazam and CBD-Rx and could explain the reduction in drop seizures seen.³³ Work by Klein et al³⁴ suggests similar findings of an increase of clobazam (1.1 to 1.2 times) and *N*-desmethylclobazam (5.2 to 8.2 times) when either CBD-Rx or stiripentol are coadministered. Conversely, Gaston et al³⁵ analyzed results of a 48-week study of 52 people with treatment-resistant epilepsy. Individuals were separated into groups based on potential drug-drug interactions: CBD-Rx with clobazam; CBD-Rx with the other interacting AEDs, rufinamide, topiramate, zonisamide, or eslicarbazepine; CBD-Rx with the other interacting AEDs and clobazam; or CBD-Rx without interacting drugs or clobazam. No difference in either seizure frequency or severity was detected between the groups.³⁵ With the conflicting evidence, it is difficult to suggest empiric dosing adjustments to clobazam when given with CBD-Rx, particularly because the increased clobazam and *N*-desmethylclobazam serum concentrations may be beneficial although the potential for adverse effects is also increased. In the patient case, it would be most prudent to administer the current dose of clobazam but monitor for adverse effects, especially somnolence, and adjust the dose if necessary.

Off-Label Use of CBD-Rx

An 84 kg, 45-year-old patient with treatment-resistant epilepsy began having seizures at age 34 after sustaining a traumatic brain injury following a motor vehicle accident. Past medications include phenytoin, carbamazepine, oxcarbazepine, valproic acid, topiramate, lamotrigine, levetiracetam, zonisamide, and tiagabine. Currently the patient takes lamotrigine and zonisamide and continues

to have 14 to 20 focal seizures with secondary generalization each month.

There is very little data to guide CBD-Rx therapy outside of LGS and DS. Much of the existing data is for other epilepsy syndromes of childhood, so there is even less information for treating adults without those syndromes. The best data comes from an open-label study of patients with treatment-resistant epilepsy. Investigators enrolled 62 adults and 70 children in a 48-week trial. Patients had a variety of epilepsy etiologies and had focal seizures, generalized seizures, or both with an average of 144.4 seizures/14 days at enrollment. At the end of the study, the mean CBD-Rx dose was 27.5 mg/kg/d. At 48 weeks, the mean number of seizures/14 days was 46.7 ($P = .0101$), and 63.9% of patients had experienced a 50% or more decrease in seizure frequency.³⁶ A second open-label study³⁷ of 22 patients with treatment-resistant epilepsy (average age 30.5 years) compared seizure activity before and after treatment with CBD-Rx (median dose 25 mg/kg/d). At baseline, patients had a mean of 12.5 seizures/mo. With CBD-Rx treatment, patients had a 71.2% reduction in seizure frequency ($P = .0009$), 80.5% reduction in seizure severity ($P < .0001$), and improvement in mood (Profile of Mood States Total Mood Disturbance score reduction of 41.3%, $P = .0026$).³⁷

Therefore, the efficacy data to guide therapy for the patient in the case is sparse. A thorough investigation of the patient's previous therapy trials should be conducted as a first step. Before deciding to start therapy, the patient should understand the lack of studies to inform care and be aware of the risks and benefits of therapy. When deciding to use CBD in an off-label manner, there are several considerations. Factors guiding treatment include the intractable nature of a patient's epilepsy, patient candidacy for and willingness to explore epilepsy surgery as an alternative to medication therapy, and ability to afford therapy or get insurance preauthorization for CBD-Rx. Particularly for adults, the cost of CBD-Rx can be problematic because the dosing is weight based.

Other open-label data shows efficacy of CBD-Rx in a variety of childhood-onset, treatment-resistant epilepsy syndromes, including data for adults.^{32,36,38-40} Adverse effects were similar to those seen in the double-blind, placebo-controlled studies. A systematic review⁴¹ in pediatric patients included the 4 randomized, placebo-controlled studies as well as 19 nonrandomized studies. The nonrandomized studies included many patients with drug-resistant epilepsy but who did not have LGS or DS. The authors⁴¹ concluded CBD-Rx was effective for reducing seizure frequency in children with drug-resistant epilepsy.

Although adverse effects are fairly well characterized from clinical trials (Table 2), questions about short- and long-term cognitive dysfunction and reproductive effects remain. A small study⁴² of 27 patients with treatment-resistant epilepsy examined the question of CBD-Rx use on cognition. This question has been raised because of the acute effects of THC on cognition.⁴² After 1 year of follow-up, investigators found no significant change in cognition.⁴³ Thus, the limited long-term information available suggests that cognitive changes are small. Little is known about the effect of CBD-Rx use on human reproduction. In monkeys and rats, male animals had decreases in testicular weights and seminiferous tubule degeneration.⁴⁴ When administered to pregnant rats and rabbits, CBD increased fetal mortality, and decreased fetal body weights were reported. At supratherapeutic doses, offspring of treated pregnant rats showed decreased growth, sexual maturation, and neurobehavioral changes.⁴⁴ Although some fetal exposure to cannabis has certainly occurred in the past, there is not a large literature that describes fetal malformation or lasting effects on these children with this exposure. More data with the use of CBD is likely to emerge, particularly if pregnant patients taking CBD are referred to the North American Antiepileptic Pregnancy Registry (<http://www.aedpregnancyregistry.org/>). Patients need education on common adverse effects and possible reproductive risks and to be amenable to follow-up liver enzyme monitoring. Additionally, patients need laboratory examinations for ALT, AST, and bilirubin before beginning therapy.

Beyond seizure control, CBD-Rx may improve quality of life for patients with treatment-resistant epilepsy. For people with epilepsy, poor seizure control, adverse effects, and anxiety and/or depression are all associated with lower quality of life.⁴⁵ Fifty-three patients with treatment refractory epilepsy were given CBD-Rx titrated to a mean maintenance dose of 27.8 mg/kg/d (which is higher than the recommended maximum dose) and followed for 1 year in an open-label fashion with the Quality of Life in Epilepsy-89 (QOLIE-89), the Profile of Mood States Total Mood Disturbance, and the Adverse Events Profile instruments as well as seizure calendars. Patients had a variety of seizure types and syndromes, including generalized and focal seizures. Only 17% of the sample had LGS and only 1.9% DS. At enrollment, 41.5% of patients had <14 seizures/2 weeks, 30.2% had 14 to 50 seizures/2 weeks, and 28.3% had more than 50 seizures/2 weeks. At the 1-year follow-up, the percentages were 62.3, 24.5, and 13.2, respectively ($P < .001$). After 1 year, the QOLIE-89 scores had improved from 49.4 at baseline to 57 ($P = .004$), the Profile of Mood States had improved from 34.7 at baseline to 25.0 ($P = .010$), and the Adverse Events Profile from 42.2 at baseline to 36.4 ($P < .001$). In the multivariate model, only 42.5% of variation in the QOLIE-89 score was explained by the variables (seizure

improvement, mood improvement, and adverse effect improvement). The authors⁴⁵ concluded that improvement in QOLIE-89 was partially improved by CBD-Rx treatment, independent of other variables. However, the limitations of this study should be noted: Particularly, it was not blinded, the CBD-Rx dose was not controlled, and some patients may have had an expectation of effect or increased study-related interactions that contributed to their improvement.

Use of Nonpharmaceutical Cannabinoids for Epilepsy

A 62-year-old patient was interested in trying non-pharmaceutical CBD for epilepsy. The patient developed epilepsy after removal of a meningioma, and the seizures had been fairly well controlled on levetiracetam 1500 mg twice daily with no adverse effects and good adherence. Since the last office visit, the patient experienced 2 focal seizures typical of previous seizures. The clinician believed it was appropriate to intensify therapy. The patient has heard CBD oil was great for epilepsy and wanted to try it instead of increasing the dose of levetiracetam or changing medicine. The patient's community pharmacist investigated prescription CBD, but it was not covered by commercial insurance.

There are many cannabinoids and many formulations of cannabinoids currently available, which can be confusing for patients and providers (Table 1). The use of nonprescription CBD and/or CBD/THC products among patients with epilepsy is likely widespread but often unreported. A survey of 39 patients who stated they used marijuana was conducted by a tertiary epilepsy center in a state where medical use of marijuana is legal. Thirty-four of these individuals indicated they used marijuana for epilepsy control; 21 of them used it multiple times daily. Thirty-one agreed or strongly agreed that it improved their seizure control.⁴⁶ It is important to emphasize that, if nonprescription CBD is used, it should be treated as a drug and dosed regularly and appropriately. There are 2 case reports of patients who were self-treating solely with CBD, who had sudden unexplained death in epilepsy, likely due to poor seizure control.⁴⁷ The unregulated nature of nonprescription CBD leads to another concern for these products: the use of CBD or THC in e-cigarettes. As of August 27, 2019, 215 cases of severe pulmonary disease were associated with the use of e-cigarettes.⁴⁸ Most of these patients reported using cannabinoid-containing products, particularly those containing THC. Lipid-laden macrophages have been recovered from bronchoalveolar lavage in many patients, thought to be caused by use of vitamin E acetate in the e-cigarettes.^{48,49} The vitamin E acetate is thought to have been added to THC-containing oil to dilute the product because it has a similar viscosity.

Although the lung injury may have been caused by the vitamin E acetate rather than THC or CBD, patients should be discouraged from using CBD- or THC-containing e-cigarette products.

Use of unregulated, nonprescription CBD may also be an issue. In 1 sample of products, investigators discovered poor quality control with some products containing more (42.9% of the products sampled) or less (26% of the products sampled) of the stated quantity of CBD.⁵⁰ Although these products should have no more than 0.3% THC, higher amounts of THC were detected in 21.43% of the products.⁵⁰ Certificates of analysis for products may be helpful in this situation; however, the certificates are not confirmed by independent testing, and the natural product may vary from batch to batch.⁵¹ Because there is no regulation of the plant source material, there could be contaminants, such as mold, pesticides, or heavy metals.⁵¹ For the patient case, choosing a higher quality CBD product is important if the patient decides to self-treat. However, there is little guidance on companies or quality assurance of products. Choosing a product with a certificate of analysis provides some assurance, but these tend to be the more expensive products. The pharmaceutical product CBD costs approximately \$32 500 annually without insurance. Appropriate dosing for an adult with nonprescription CBD could rival these costs.⁵² If the prescriber is in agreement for the use of CBD for this patient, it may be possible to get insurance preauthorization for off-label use of prescription CBD, which would be preferable to nonprescription CBD.

The legal aspects of CBD and THC use should also be considered. In 2018, Congress approved the Agriculture Improvement Act of 2018, which removed hemp products containing less than 0.3% THC from the Controlled Substances Act.⁵³ The effects of this bill allow CBD-containing products to be sold without a prescription in most states. As of May 4, 2020, Idaho, Kansas, Nebraska, and South Dakota prohibit sale of these products.⁵⁴ Despite some state laws that allow for THC sales, marijuana and its derivatives remain controlled substances at the federal level.⁵³ The FDA initially placed CBD-Rx into schedule V of the Controlled Substances Act in 2018.⁵⁵ However, on April 6, 2020, it was descheduled.⁵⁶ There are reports of patients with failed urine drug tests when using CBD, including the prescription product. Hypotheses advanced to explain this are that nonprescription CBD products may be mislabeled or that THC can accumulate in the body, so even consuming small amounts, over time, a positive test may be seen.^{3,51} The patient above needs to consider legal and employment implications of using any CBD product.

Conclusion

A prescription CBD product offers a new therapeutic option for patients with the very treatment-resistant epilepsy syndromes LGS and DS. Use of CBD outside of these indications is less clear. For at least some other childhood-onset epilepsy syndromes, there is some evidence of efficacy and more trials ongoing. Use in adult patients as a monotherapy or adjunctive therapy has not been examined in any systematic fashion to date. Based on the proposed mechanism of action of CBD, it is likely to be effective for focal epilepsies, but this remains to be proven. Nonprescription CBD products have purity and product variability concerns and their use cannot be condoned at this time.

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