Epilepsy Currents
2019, Vol. 19(2) 93-95

DOI: 10.1177/1535759719835671
journals.sagepub.com/home/epi
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Don't Fear the Reefer—Evidence Mounts for Plant-Based Cannabidiol as Treatment for Epilepsy

Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome

Devinsky O, Patel AD, Cross JH, et al; GWPCARE3 Study Group. *N Engl J Med*. 2018;378:1888-1897. doi:10.1056/NEJMoa1714631

Background: Cannabidiol has been used for treatment-resistant seizures in patients with severe early-onset epilepsy. We investigated the efficacy and safety of cannabidiol added to a regimen of conventional antiepileptic medication to treat drop seizures in patients with the Lennox-Gastaut syndrome, a severe developmental epileptic encephalopathy. Methods: In this double-blind, placebo-controlled trial conducted at 30 clinical centers, we randomly assigned patients with the Lennox-Gastaut syndrome (age range, 2-55 years) who had had 2 or more drop seizures per week during a 28-day baseline period to receive cannabidiol oral solution at a dose of 20 mg/kg of body weight (20-mg cannabidiol group) or 10 mg/kg (10-mg cannabidiol group) or matching placebo, administered in 2 equally divided doses daily for 14 weeks. The primary outcome was the percentage change from baseline in the frequency of drop seizures (average per 28 days) during the treatment period. Results: A total of 225 patients were enrolled; 76 patients were assigned to the 20-mg cannabidiol group, 73 to the 10-mg cannabidiol group, and 76 to the placebo group. During the 28-day baseline period, the median number of drop seizures was 85 in all trial groups combined. The median percentage reduction from baseline in drop seizure frequency during the treatment period was 41.9% in the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group, and 17.2% in the placebo group ($P = .005$ for the 20-mg cannabidiol group vs placebo group, and $P = .002$ for the 10-mg cannabidiol group vs placebo group). The most common adverse events among the patients in the cannabidiol groups were somnolence, decreased appetite, and diarrhea; these events occurred more frequently in the higher dose group. Six patients in the 20-mg cannabidiol group and 1 patient in the 10-mg cannabidiol group discontinued the trial medication because of adverse events and were withdrawn from the trial. Fourteen patients who received cannabidiol (9%) had elevated liver aminotransferase concentrations. Conclusions: Among children and adults with the Lennox-Gastaut syndrome, the addition of cannabidiol at a dose of 10 or 20 mg/kg/d to a conventional antiepileptic regimen resulted in greater reductions in the frequency of drop seizures than placebo. Adverse events with cannabidiol included elevated liver aminotransferase concentrations. (Funded by GW Pharmaceuticals; GWPCARE3 ClinicalTrials.gov number, NCT02224560.)

Long-Term Safety and Treatment Effects of Cannabidiol in Children and Adults With Treatment-Resistant Epilepsies: Expanded Access Program Results

Szaflarski JP, Bebin EM, Comi AM, et al; CBD EAP Study Group. *Epilepsia*. 2018;59(8):1540-1548. doi:10.1111/epi.14477

Objective: Since 2014, cannabidiol (CBD) has been administered to patients with treatment-resistant epilepsies (TREs) in an ongoing expanded access program (EAP). We report interim results on the safety and efficacy of CBD in EAP patients treated through December 2016. Methods: Twenty-five US-based EAP sites enrolling patients with TRE taking stable doses of antiepileptic drugs (AEDs) at baseline were included. During the 4-week baseline period, parents/caregivers kept diaries of all countable seizure types. Patients received oral CBD starting at 2 to 10 mg/kg/d, titrated to a maximum dose of 25 to 50 mg/kg/d. Patient visits were every 2 to 4 weeks through 16 weeks and every 2 to 12 weeks thereafter. Efficacy end points included the percentage change from baseline in median monthly convulsive and total seizure frequency and percentage of patients with $\geq$50%, $\geq$75%, and 100% reductions in seizures versus baseline. Data were analyzed descriptively for the efficacy analysis set and using the last-observation-carried-forward method to account for missing data. Adverse events (AEs) were documented at each visit. Results: Of 607 patients in the safety data set, 146 (24%) withdrew; the most common reasons were lack of efficacy (89 [15%]) and AEs (32 [5%]). Mean age was 13 years (range, 0.4-62). Median number of concomitant AEDs was 3 (range, 0-10). Median CBD dose was 25 mg/kg/d; median treatment duration was 48 weeks. Add-on CBD reduced median monthly

convulsive seizures by 51% and total seizures by 48% at 12 weeks; reductions were similar through 96 weeks. Proportion of patients with ≥50%, ≥75%, and 100% reductions in convulsive seizures were 52%, 31%, and 11%, respectively, at 12 weeks, with similar rates through 96 weeks. Cannabidiol was generally well tolerated; most common AEs were diarrhea (29%) and somnolence (22%). Significance: Results from this ongoing EAP support previous observational and clinical trial data, showing that add-on CBD may be an efficacious long-term treatment option for TRE.

Randomized, Dose-Ranging Safety Trial of Cannabidiol in Dravet Syndrome

Devinsky O, Patel AD, Thiele EA, et al; GWPCARE1 Part A Study Group. *Neurology*. 2018;90(14):e1204-e1211. doi:10.1212/WNL.0000000000005254

Objective: To evaluate the safety and preliminary pharmacokinetics of a pharmaceutical formulation of purified cannabidiol (CBD) in children with Dravet syndrome. Methods: Patients aged 4 to 10 years were randomized 4:1 to CBD (5, 10, or 20 mg/kg/d) or placebo taken twice daily. The double-blind trial comprised 4-week baseline, 3-week treatment (including titration), 10-day taper, and 4-week follow-up periods. Completers could continue in an open-label extension. Multiple pharmacokinetic blood samples were taken on the first day of dosing and at end of treatment for measurement of CBD, its metabolites 6-OH-CBD, 7-OH-CBD, and 7-COOH-CBD, and antiepileptic drugs (AEDs; clobazam and metabolite *N*-desmethylclobazam [N-CLB], valproate, levetiracetam, topiramate, and stiripentol). Safety assessments were clinical laboratory tests, physical examinations, vital signs, electrocardiograms, adverse events (AEs), seizure frequency, and suicidality. Results: Thirty-four patients were randomized (10, 8, and 9 to the 5, 10, and 20 mg/kg/d CBD groups and 7 to placebo); 32 (94%) completed treatment. Exposure to CBD and its metabolites was dose proportional ($AUC_{0\text{-}t}$). Cannabidiol did not affect concomitant AED levels, apart from an increase in N-CLB (except in patients taking stiripentol). The most common AEs on CBD were pyrexia, somnolence, decreased appetite, sedation, vomiting, ataxia, and abnormal behavior. Six patients taking CBD and valproate developed elevated transaminases; none met criteria for drug-induced liver injury and all recovered. No other clinically relevant safety signals were observed. Conclusions: Exposure to CBD and its metabolites increased proportionally with dose. An interaction with N-CLB was observed, likely related to CBD inhibition of cytochrome P450 subtype 2C19. Cannabidiol resulted in more AEs than placebo but was generally well tolerated. Classification of Evidence: This study provides class I evidence that for children with Dravet syndrome, CBD resulted in more AEs than placebo but was generally well tolerated.

Commentary

The idea of using cannabis for medicinal purposes is not new, having been reported in ancient texts of China and Mesopotamia for treatment of epilepsy, spasticity, and depression and described somewhat more scientifically by O'Shaughnessy in the early 1800s.[1,2] Today, the Internet is riddled with stories proclaiming the miracle cure cannabis and, in particular, phytocannabinoid cannabidiol (CBD) can be for people with epilepsy. However, the initial popularity of CBD as a treatment for epilepsy lacked solid scientific support, stoking skepticism in the medical community. Notably, lacking was quality evidence for efficacy and safety and a standardized, regulated form of treatment. To date, data have been largely observational, open label, without standardization, and potentially biased. Indeed, families that moved to Colorado (one of the first states to allow medical cannabis) to start CBD oils for intractable epilepsy were significantly more likely to report efficacy compared to patients already living in the state, underscoring the bias which likely pervaded many early observational studies.[3] Recently, the tide has turned for CBD and cannabis as a treatment, with evidence from several well-designed trials of a plant-based CBD (Epidiolex, Greenwich Biosciences, Carlsbad, CA, USA) beginning to provide the data needed to allow CBD to take its place as a viable epilepsy treatment, while paving the road for many other compounds from the cannabis plant to be studied in the future.

Logically, the initial question is how efficacious is CBD for seizure control? Several recent randomized, double-blind, placebo controlled trials have provided that answer. Although CBD is not the panacea the Internet has proclaimed, there is solid evidence that it is effective, particularly for drop (atonic, tonic, tonic–clonic) seizures. Devinsky et al reported a statistically significant reduction of drop seizures in patients with Lennox-Gastaut syndrome (LGS) using both 20 and 10 mg/kg/d dosing of CBD compared to placebo. The 41.9% reduction seen in the 20 mg/kg/d group (vs 17.2% placebo) compares reasonably to other drugs approved for LGS, namely, rufinamide and clobazam.[4,5] Although these studies were conducted with slightly different designs, rufinamide demonstrated a 42.5% median reduction in drop seizures versus placebo (−1.4%), while clobazam reported mean weekly drop seizure reduction of 68% using high dose versus placebo (−12.1%). Taken at face value, one might argue CBD is comparatively less effective, though we must question what impact the placebo effect had on this trial. Perhaps more clinically relevant are the "super-responders," those with >75% reduction or seizure freedom. During the 14-week treatment phase, 25% of patients on 20 mg/kg/d and 11% on 10 mg/kg/d CBD had >75% reduction in seizures, while 5% of patients were free of drop seizures during the maintenance phase. This compares favorably to 21.9% of patients on rufinamide with >75%

reduction, though not as well as 63% of patients on high-dose clobazam who experienced >75% reduction, nor the 25% who were reported seizure-free.

Patients are particularly partial to CBD because of its natural origin, which is interpreted to suggest a favorable adverse effect profile. However, it is not without adverse effects, with somnolence, decreased appetite, and diarrhea being the most common. The contribution of concomitant drugs to these adverse effects must be acknowledged, as many patients with significant somnolence were on clobazam. Additional safety studies of CBD by Devinsky et al demonstrated a >166% increase in the active metabolite, *N*-desmethylclobazam, when clobazam was taken concomitantly with CBD. Many patients experienced less sedation with decreased clobazam dosing, underscoring the importance of this interaction. Serious adverse effects (SAEs) are relatively rare, with 3% experiencing at least 1 SAE deemed related to CBD treatment in the randomized trial, which is similar to the 8% rate in the clobazam trial. In addition, the data on tolerability of adverse effects are encouraging, with 4.7% of patients in the CBD trial discontinuing for AE compared with 13% in the clobazam trial. Importantly, many of the patients withdrawing from this CBD trial did so because of elevation of liver enzymes that occurred more often in patients treated with concomitant valproate, again underscoring the importance of understanding significant medication interactions.

Perhaps most promising is long-term safety and efficacy data for intractable epilepsies beyond LGS and Dravet syndrome, as suggested by analysis from the open-label expanded access program. Similar to the randomized trials, participants experienced a median 51% reduction in convulsive seizures and this response was maintained through 96 weeks consistent with a low likelihood of pharmacologic tolerance. The impact of concomitant medications was further characterized, with 38% of patients on combined CBD and clobazam experiencing somnolence compared to only 14% without clobazam. While the expanded access program allowed for CBD dosing as high as 50 mg/kg/d, the authors did not report whether increasing dose provided additional efficacy. Finally, while total seizures were reduced to a similar degree as convulsive and drop seizures in these studies, the true efficacy for nonconvulsive seizures remains unclear, as these protocols were not designed to assess this end point.

Following years of speculation and studies marred by observational bias, the horse is finally catching up to the cart as it pertains to CBD and epilepsy. We now have reliable data that plant-derived CBD is effective for the treatment of various epilepsy and seizure types. While CBD is not the cure-all early Internet reports suggested, it has a place on par with other pharmaceuticals that have come before it. In fact, it is possible that other phytocannabinoids within the cannabis plant are responsible for the superb efficacy reports that preceded these studies, but only time and further research of these isolated compounds will tell. With a favorable AE profile and long-term, sustained efficacy, CBD is a reasonable treatment consideration for a wide range of patients with epilepsy. Practitioners must be cautious not to extrapolate data from this single version of CBD to other widely available formulations that lack the rigorous standards of production and purity, as their safety and efficacy have not been established. However, the body of evidence increasingly demonstrates that there is more to learn and less to fear from CBD as a treatment for epilepsy.

By M. Scott Perry

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