

# Exhibit D

[Epilepsy Behav.](#) 2013 Dec;29(3):574-7. doi: 10.1016/j.yebeh.2013.08.037.

## **Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy.**

[Porter BE<sup>1</sup>](#), [Jacobson C.](#)  
[Author information](#)

### **Abstract**

Severe childhood epilepsies are characterized by frequent seizures, neurodevelopmental delays, and impaired quality of life. In these treatment-resistant epilepsies, families often seek alternative treatments. This survey explored the use of cannabidiol-enriched cannabis in children with treatment-resistant epilepsy. The survey was presented to parents belonging to a Facebook group dedicated to sharing information about the use of cannabidiol-enriched cannabis to treat their child's seizures. Nineteen responses met the following inclusion criteria for the study: a diagnosis of epilepsy and current use of cannabidiol-enriched cannabis. Thirteen children had Dravet syndrome, four had Doose syndrome, and one each had Lennox-Gastaut syndrome and idiopathic epilepsy. The average number of antiepileptic drugs (AEDs) tried before using cannabidiol-enriched cannabis was 12. **Sixteen (84%) of the 19 parents reported a reduction in their child's seizure frequency while taking cannabidiol-enriched cannabis. Of these, two (11%) reported complete seizure freedom, eight (42%) reported a greater than 80% reduction in seizure frequency, and six (32%) reported a 25-60% seizure reduction.** Other beneficial effects included increased alertness, better mood, and improved sleep. Side effects included drowsiness and fatigue. Our survey shows that parents are using cannabidiol-enriched cannabis as a treatment for their children with treatment-resistant epilepsy. Because of the increasing number of states that allow access to medical cannabis, its use will likely be a growing concern for the epilepsy community. Safety and tolerability data for cannabidiol-enriched cannabis use among children are not available. Objective measurements of a standardized preparation of pure cannabidiol are needed to determine whether it is safe, well tolerated, and efficacious at controlling seizures in this pediatric population with difficult-to-treat seizures.

**CONTINUED ON NEXT PAGE**

[Epilepsy Behav.](#) 2012 Dec;25(4):563-6. doi: 10.1016/j.yebeh.2012.09.024. Epub 2012 Nov 13.

# Seizure exacerbation in two patients with focal epilepsy following marijuana cessation.

[Hegde M<sup>1</sup>](#), [Santos-Sanchez C](#), [Hess CP](#), [Kabir AA](#), [Garcia PA](#).

[Author information](#)

## Abstract

While animal models of epilepsy suggest that exogenous cannabinoids may have anticonvulsant properties, scant evidence exists for these compounds' efficacy in humans. **Here, we report on two patients whose focal epilepsy was nearly controlled through regular outpatient marijuana use. Both stopped marijuana upon admission to our epilepsy monitoring unit (EMU) and developed a dramatic increase in seizure frequency documented by video-EEG telemetry.** These seizures occurred in the absence of other provocative procedures, including changes to anticonvulsant medications. We review these cases and discuss mechanisms for the potentially anticonvulsant properties of cannabis, based on a review of the literature.

[J Clin Pharmacol](#). 1981 Aug-Sep;21(8-9 Suppl):417S-427S.

# Hypnotic and antiepileptic effects of cannabidiol.

[Carlini EA](#), [Cunha JM](#).

## Abstract

Clinical trials with cannabidiol (CBD) in healthy volunteers, insomniacs, and epileptic patients conducted in the authors' laboratory from 1972 up to the present are reviewed. Acute doses of cannabidiol ranging from 10 to 600 mg and chronic administration of 10 mg for 20 days or 3 mg/kg/day for 30 days did not induce psychologic or physical symptoms suggestive of psychotropic or toxic effects; however, several volunteers complained of somnolence. Complementary laboratory tests (EKG, blood pressure, and blood and urine analysis) revealed no sign of toxicity. Doses of 40, 80, and 160 mg cannabidiol were compared to placebo and 5 mg nitrazepam in 15 insomniac volunteers. Subjects receiving 160 mg cannabidiol reported having slept significantly more than those receiving placebo; the volunteers also reported significantly less dream recall; with the three doses of cannabidiol than with placebo. **Fifteen patients suffering from secondary generalized epilepsy refractory to known antiepileptic drugs received either 200 to 300 mg cannabidiol daily or placebo for as long as 4.5 months. Seven out of the eight epileptics receiving cannabidiol had improvement of their disease state, whereas only one placebo patient improved.**

Continued on next page

[Pharmacology](#). 1980;21(3):175-85.

## Chronic administration of cannabidiol to healthy volunteers and epileptic patients.

[Cunha JM](#), [Carlini EA](#), [Pereira AE](#), [Ramos OL](#), [Pimentel C](#), [Gagliardi R](#), [Sanvito WL](#), [Lander N](#), [Mechoulam R](#).

### Abstract

In phase 1 of the study, 3 mg/kg daily of cannabidiol (CBD) was given for 30 days to 8 healthy human volunteers. Another 8 volunteers received the same number of identical capsules containing glucose as placebo in a double-blind setting. Neurological and physical examinations, blood and urine analysis, ECG and EEG were performed at weekly intervals. In phase 2 of the study, 15 patients suffering from secondary generalized epilepsy with temporal focus were randomly divided into two groups. Each patient received, in a double-blind procedure, 200-300 mg daily of CBD or placebo. The drugs were administered for along as 4 1/2 months. Clinical and laboratory examinations, EEG and ECG were performed at 15- or 30-day intervals. Throughout the experiment the patients continued to take the antiepileptic drugs prescribed before the experiment, although these drugs no longer controlled the signs of the disease. All patients and volunteers tolerated CBD very well and no signs of toxicity or serious side effects were detected on examination. **4 of the 8 CBD subjects remained almost free of convulsive crises throughout the experiment and 3 other patients demonstrated partial improvement in their clinical condition. CBD was ineffective in 1 patient.** The clinical condition of 7 placebo patients remained unchanged whereas the condition of 1 patient clearly improved. The potential use of CBD as an antiepileptic drug and its possible potentiating effect on other antiepileptic drugs are discussed.

[J Clin Pharmacol](#). 1981 Aug-Sep;21(8-9 Suppl):437S-448S.

## The cannabinoids as potential antiepileptics.

[Karler R](#), [Turkanis SA](#).

### Abstract

Comparative studies of the anticonvulsant properties of the cannabinoids and prototype antiepileptic drugs in numerous animal seizure models demonstrate that (1) as an anticonvulsant, cannabidiol (CBD), in contrast to delta 9-tetrahydrocannabinol (THC), is relatively selective in terms of both central nervous system (CNS), depressant and excitatory properties; (2) the potency of cannabidiol, unlike that of phenytoin and phenobarbital, varies greatly with the species; (3) the large potency difference between the cannabinoids and the antiepileptics in the mouse appears to be due to dispositional differences, because brain concentrations of all the drugs are very similar; (4) tolerance to the anticonvulsant properties of cannabidiol is not a prominent feature; in three seizure models, tolerance developed in one, but "reverse tolerance" developed in the other two; and (5) the results of a study of the electrophysiologic mechanisms of action indicate that cannabidiol produces some unique effects and that its spectrum of antiepileptic activity may be different from that of the prototype drugs. The anticonvulsant nature of cannabidiol suggests that it has a therapeutic potential in at least three of the four major types of epilepsy: grand mal, cortical focal, and complex partial seizures.