FULL-LENGTH ORIGINAL RESEARCH

Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex

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Epilepsia, 57(10):1617–1624, 2016
doi: 10.1111/epi.13499

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Summary

Objective: Tuberous sclerosis complex (TSC) is an autosomal-dominant genetic disorder with highly variable expression. The most common neurologic manifestation of TSC is epilepsy, which affects approximately 85% of patients, 63% of whom develop treatment-resistant epilepsy. Herein, we evaluate the efficacy, safety, and tolerability of cannabidiol (CBD), a nonpsychoactive compound derived from the marijuana plant, as an adjunct to current antiepileptic drugs in patients with refractory seizures in the setting of TSC.

Methods: Eighteen of the 56 patients who have enrolled in our current expanded-access study of cannabidiol for patients with treatment-resistant epilepsy carry a diagnosis of TSC. After an initial baseline period of 1 month, patients began treatment with CBD. The initial dose of 5 mg/kg/day was increased by 5 mg/kg/day every week up to a maximum dose of 50 mg/kg/day, if tolerated. Weekly seizure frequencies, percent change in seizure frequencies, and responder rates were calculated during the 2nd, 3rd, 6th, 9th, and 12th month of treatment with CBD.

Results: The median weekly seizure frequency during the baseline period was 22.0 (interquartile range [IQR] 14.8–57.4), which decreased to 13.3 (IQR 5.1–22.1) after 3 months of treatment with cannabidiol. The median percent change in total weekly seizure frequency was −48.8% (IQR −69.1% to −11.1%) after 3 months of treatment. The 50% responder rates over the course of the study were 50%, 50%, 38.9%, 50%, and 50% after 2, 3, 6, 9, and 12 months of treatment with CBD, respectively. In patients taking clobazam concurrently with CBD (n = 12), the responder rate after 3 months of treatment was 58.3%, compared to 33.3% in patients not taking clobazam (n = 6). Twelve (66.7%) of 18 patients in this study experienced at least one adverse event thought possibly related to CBD; the most common adverse events were drowsiness (n = 8, 44.4%), ataxia (n = 5, 27.8%), and diarrhea (n = 4, 22.2%).

Significance: Although double-blind, placebo-controlled trials are still necessary, these findings suggest that cannabidiol may be an effective and well-tolerated treatment option for patients with refractory seizures in TSC.

KEY WORDS: Tuberous sclerosis complex, Cannabidiol, Efficacy, Tolerability, Seizures.

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with highly variable expression. TSC is characterized by the presence of hamartomas in almost every organ system, including angiomyolipomas in the kidneys, lymphangioleiomyomatosis in the lungs, rhabdomyomas in the heart, angiofibromas on the face, and tubers and subependymal nodules in the brain. TSC is caused by a mutation in the *TSC1* and *TSC2* genes, which encode for the hamartin and tuberin proteins, respectively. Normally, these proteins form a complex that acts as a tumor suppressor and a central regulator in the mammalian target of rapamycin (mTOR) signaling cascade.[1,2]

Accepted July 20, 2016.
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Key Points

- Patients with refractory seizures in the setting of TSC had a median percent change in weekly seizure frequency of −48.8% after 3 months of treatment with CBD
- The responder rate after 3 months of treatment with CBD was 50%
- After 3 months of treatment with CBD, the median weekly seizure frequency decreased for all seizure types experienced by patients in this study
- Parents of patients reported cognitive gains in 85.7% of cases and behavioral improvements in 66.7% of cases with baseline cognitive or behavioral problems
- Most adverse events experienced in this study were temporary, of mild severity, and resolved through dose adjustments of CBD or concomitant antiepileptic drugs

The most common neurologic symptom of TSC is epilepsy, which affects approximately 85% of patients. Of TSC patients with epilepsy, approximately 63% develop treatment-resistant epilepsy (as opposed to 23% in the general epilepsy population); 82% experience their first seizure within the first 3 years of life, and 53% have more than one seizure type.[3] Fifty percent of patients with TSC have global intellectual impairment,[1] and early onset refractory seizures put patients at greater risk for developing cognitive impairment.[3] Although epilepsy remission is associated with an improved cognitive outcome, only 19% of patients with refractory epilepsy achieve seizure remission.[3] Many of these patients have tried most or all available treatments and experienced inadequate seizure control and/or behavioral side effects. There is a need for more effective antiepileptic drugs (AEDs) with more favorable adverse event profiles.

Cannabidiol (CBD) is a nonpsychoactive compound derived from the marijuana plant that has gained significant media attention recently.[4–9] Several preclinical[10–17] and clinical[6,18,19] studies suggest that CBD has anticonvulsant effects and is well tolerated. The Massachusetts General Hospital is currently participating in an institutional review board (IRB)– and U.S. Food and Drug Administration (FDA)–approved expanded-access study for CBD in the treatment of refractory seizures. Herein, we evaluate the efficacy, safety, and tolerability of CBD as an adjunct to current antiepileptic drugs (AEDs) in patients enrolled in our expanded access study with refractory seizures in the setting of TSC.

Methods

Study design

Of the 56 patients who consented and enrolled in our current IRB- and FDA-approved expanded-access study of CBD under Investigational New Drug (IND) 119876, 18 patients have TSC. Five of these patients were included as part of the multicenter analysis of CBD expanded-access programs in Devinsky et al. Details of the epilepsy and treatment histories for each patient were obtained through available electronic medical records.

Inclusion criteria for participation in the expanded-access program and for this study require a diagnosis of TSC and drug-resistant epilepsy, taking between one and seven AEDs at stable doses for a minimum of 2 weeks, and stable vagus nerve stimulation (VNS) settings and ketogenic diet ratios for a minimum of 4 weeks. Exclusion criteria for this study include allergies to ingredients in the study drug solution; unstable hepatic, hematologic, renal, cardiovascular, gastrointestinal, or pulmonary diseases; use of investigational drugs or devices <30 days prior to study entry; significant abnormal laboratory values; history of drug use; pregnancy; current systemic steroid use; or poor compliance.

During an initial baseline period of 1 month, all patients and/or parents reported the number of seizures recorded each day; seizure types reported include complex partial seizures, complex partial seizures with secondary generalization, atonic seizures, tonic seizures, tonic–clonic seizures, and epileptic spasms. An estimated number of atypical absence seizures was also included in these reports. Patients subsequently began treatment with GWP42003-P, a 99% pure CBD extract in a 100 mg/ml sesame oil–based oral solution provided by GW Pharmaceuticals, at a dose of 5 mg/kg/day and given in two divided doses. This dose was increased by 5 mg/kg/day every week up to an initial maximum dose of 25 mg/kg/day. For subjects who continued to have seizures and tolerated CBD at 25 mg/kg/day, the dose was increased to a maximum dose of 50 mg/kg/day at a maximum rate of 5 mg/kg/day each week. At each clinic visit, patients or parents returned all logs of recorded seizures since the last clinic visit; concomitant AEDs, changes in cognition and behavior, adverse events, and epilepsy-related hospitalizations were also reviewed at each clinic visit. Changes in the dose of concomitant AEDs were made as clinically indicated. Doses of concomitant AEDs were held constant over the first 3 months, with the exception of clobazam doses, which were reduced due to adverse events or elevated plasma levels of clobazam and N-desmethylclobazam in the 12 patients taking clobazam concurrently. After the third month of CBD treatment, doses of CBD and concomitant AED were changed monthly in nearly all patients in order to optimize seizure control.

Analysis

Weekly seizure frequencies during the 2nd, 3rd, 6th, 9th, and 12th months of treatment with CBD were calculated for all patients for each seizure type and the total number of seizures.

$$\text{Weekly Seizure Frequency}_{\text{Month x}} = \frac{(\text{Number of Seizures}_{\text{Month x}})}{(\text{Number of Days}_{\text{Month x}})} \times 7$$

Due to the large variation in absolute number of seizures between each patient, reduction in seizure frequency was also analyzed by calculating percent change in seizure frequency for each seizure type and the total number of seizures during the 2nd, 3rd, 6th, 9th, and 12th months of treatment with CBD. Percent change at each time point reflects reported seizure frequency over the past month relative to baseline.

$$\text{Percent Change in Seizure Frequency}_{\text{Month x}} = \frac{(\text{Weekly Seizure Frequency}_{\text{Month x}}) - (\text{Weekly Seizure Frequency}_{\text{Baseline}})}{(\text{Weekly Seizure Frequency}_{\text{Baseline}})}$$

Using the percent change in seizure frequency at each time point, patients were defined as responders if they had a >50% reduction in total seizure frequency. Patients who exited the study before a certain time point or patients who lacked follow-up to a given time point were not included in any calculations for the corresponding month.

Results

Eighteen patients with TSC enrolled in the expanded access study for cannabidiol in the treatment of refractory epilepsy between May 7, 2014 and August 20, 2015. Patients entered the study at different times and some have exited; therefore, not all patients in this study have been treated with CBD for 12 months. Based on their latest available clinic visit date, all 18 patients have been in the study for at least 6 months, whereas 16 have been in the study for at least 9 months and 8 have been in the study for at least 12 months.

As seen in Table 1, 9 (50%) of these 18 patients are male and 9 (50%) of 18 are female. The age range of these patients is 2–31 years with an average age of 14 years. Of the 14 patients with genetic testing, all have an identifiable mutation; 4 (22%) have a family history of TSC, 7 (50%) have a disease-associated *TSC1* mutation, and 7 (50%) have a disease-associated *TSC2* mutation. Age of seizure onset ranges from 1 month to 6 years, with an average of 1.19 years; however, the most common age of seizure onset is 3 months (n = 4, 22%). Physician- and parent-observed developmental delays were reported in 14 (78%) of 18 patients; 10 (55.6%) of 18 patients underwent neuropsychological testing, of whom 6 (60%) were cognitively impaired (IQ < 70). In addition, physician- and parent-observed behavioral problems were reported in 9 (50%) of 18 patients in this study. Ten (55.6%) of 18 patients in this study have a history of autism.

Patients participating in this study have relatively complex epilepsy histories, given that treatment-resistant seizures are so common in the TSC population. As shown in Table S1, 13 (72%) of 18 patients have more than one seizure type; seizure types experienced include complex partial seizures (n = 13, 72%), tonic seizures (n = 7, 39%), tonic–clonic seizures (n = 6, 33%), epileptic spasms (n = 4, 22%), complex partial seizures with secondary generalization (n = 4, 22%), atonic seizures (n = 4, 22%), and atypical absence seizures (n = 4, 22%). Treatment histories of these patients are also quite extensive, with 12 (67%) undergoing epilepsy surgery, 11 (61%) trying a vagus nerve stimulator, and 11 (61%) trying dietary therapy. With respect to medical treatments, patients in this study have tried between 4 and 11 AEDs with a median of 7; upon enrollment, patients were currently taking between 1 and 7 AEDs with a median of 3. The most common AEDs tried among patients in this study during their lifetime include clobazam (n = 18, 100%), lacosamide (n = 16, 89%), levetiracetam (n = 14, 78%), valproic acid (n = 13, 82%), lamotrigine (n = 10, 56%), and vigabatrin (n = 9, 50%); however, the most common concomitant AEDs during this study include lacosamide (n = 14, 78%), clobazam (n = 10, 56%), levetiracetam (n = 7, 39%), lamotrigine (n = 5, 28%), valproic acid (n = 3, 17%), and rufinamide (n = 3, 17%).

The median total weekly seizure frequency during the 4-week baseline period was 22.0 (interquartile range [IQR] 14.8–57.4). This value continued to decrease throughout the first 12 months of treatment with CBD (with the exception of a slight increase between 9 and 12 months likely due to a decrease in sample size and/or changes in concomitant medications). Shown in the box plot in Figure 1, the median total weekly seizure frequency decreased to 14.9 (IQR 5.7–22.0) after 2 months of treatment, 13.2 (IQR 5.06–22.1) after 3 months of treatment, 9.7 (IQR 5.4–21.4) after 6 months of treatment, 7.7 (IQR 5.1–34.9) after 9 months of treatment, and 8.0 (IQR 3.7–47.7) after 12 months of treatment.

After calculating the percent change in weekly seizure frequency, it can be seen that there is a general decreasing trend across time, indicating a decrease in absolute weekly

Table 1. Demographics and TSC syndrome–related histories

Case no.	Sex	Age	Mutation	Age seizure onset (months)	Family history of TSC	Developmental delays	Behavioral problems	History of autism
1	M	14	*TSC1*	60	No	No[a]	Yes	No
2	M	7	*TSC1*	1	Yes	Yes[b]	Yes	No
3	M	18	Not tested	72	No	No[a]	No	Yes
4	M	15	*TSC2*	8	No	Yes[b]	No	Yes
5	F	13	*TSC2*	3	No	Yes[b]	No	Yes
6	M	3	*TSC1*	3	No	Yes	No	No
7	F	9	Not tested	5	No	Yes	Yes	No
8	M	9	*TSC2*	4	No	Yes	No	Yes
9	F	13	*TSC2*	1	No	No[a]	Yes	No
10	M	23	Not tested	48	No	No[a]	No	No
11	F	2	*TSC2*	1	No	Yes	Yes	No
12	F	18	*TSC1*	8	No	Yes[b]	No	Yes
13	F	3	*TSC1*	16	Yes	Yes	No	No
14	F	7	*TSC2*	5	No	Yes[b]	Yes	Yes
15	M	31	*TSC1*, *TSC2*[c]	6	Yes	Yes	Yes	Yes
16	F	26	*TSC1*	10	No	Yes	Yes	Yes
17	F	13	Not tested	3	Yes	Yes[b]	No	Yes
18	M	29	*TSC2*	3	No	Yes	Yes	Yes

[a]Patients who underwent neuropsychological testing and have no cognitive impairment (IQ $\geq$ 70).
[b]Patients who underwent neuropsychological testing and have cognitive impairment (IQ $<$ 70).
[c]Patient has a maternal *TSC2* mutation of unknown clinical significant and a sporadic disease-associated *TSC1* mutation.

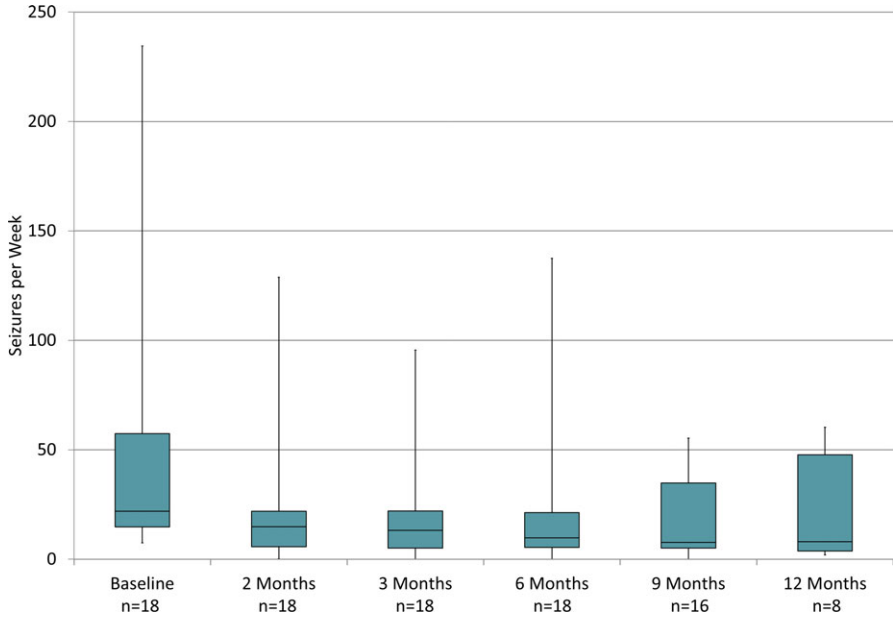

Figure 1.
Weekly total seizure frequency at baseline and after 2, 3, 6, 9, and 12 months of treatment with CBD. The box plots show minimum, first quartile, median, third quartile, and maximum. The increase in interquartile range between 6 months and 12 months and the increase in median seizure frequency between month 9 and month 12 is most likely due to a decrease in sample size.

seizure frequency (Table 2). Of note, after 3 months of treatment with CBD, four patients (2, 7, 9, and 16) had a percent decrease in seizures of >80%, and two patients (2 and 9) had a percent decrease in seizures of >90%. Patient 9 became seizure-free after 3 months of treatment and remained seizure-free until the 12th month of treatment when seizures recurred due to an attempted taper in lacosamide.

After 3 months of treatment with CBD, the median weekly seizure frequency decreased for all seizure types experienced by patients in this study. Based on the calculated median percent change in seizure frequency after 3 months of treatment for each seizure type, the greatest reduction in seizures was observed in tonic–clonic seizures (−91.4%, n = 6, IQR −100% to −13.9%), followed by epileptic spasms (−87.5%, n = 4, IQR −100% to −68.4%), atonic seizures (−86.5%, n = 4, IQR −100% to −49.4%), complex partial seizures (−59.3%, n = 13, IQR −80.2% to −9.8%), tonic seizures (−48.2%, n = 7, IQR −77.6% to 34.3%), and, finally, complex partial seizures with

Table 2. Percent change in seizure frequency after treatment with cannabidiol

Case no.	Month 2	Month 3	Month 6	Month 9	Month 12
1	−58.1	−63.2	−31.5	−55.6	−46.1
2	−93.3	−93.7	−97.3	−96.6	−96.4
3	−55.8	−71.1	−91.1	−71.9	−86.6
4	−22.2	−15.0	−4.5	−24.6	Exit
5	−25.9	−39.2	−36.4	−41.8	−28.1
6	−38.4	−33.5	−34.0	29.9	68.6
7	−74.1	−80.2	−79.6	−75.2	−66
8	26.8	−5.9	35.3	−49.7	−49.1
9	−99.7	−100.0	−100.0	−100.0	−96.2
10	−45.1	−9.8	18.8	−33.1	Exit
11	40.8	−47.0	−34.3	−100.0	LFU
12	3.0	0.6	−14.6	−3.2	LFU
13	−52.8	−55.7	−74.1	−54.2	LFU
14	−73.8	−56.0	−46.2	−33.3	LFU
15	77.6	62.9	29.3	−40.1	LFU
16	−87.3	−86.7	−64.1	−63.7	LFU
17	−78.7	−50.6	−68.1	LFU	LFU
18	60.5	78.0	−23.7	LFU	LFU
Median	−48.9	−48.8	−35.4	−51.9	−57.5

Exit, patients who exited the study; LFU, lack follow-up.
All patients with numbers entered were still taking CBD the corresponding month.

secondary generalization (−38.6%, n = 4, IQR −53.6% to 1.6%).

Using responder rates after 3 months of treatment as a measure of efficacy, the effect of CBD on each seizure type follows a somewhat similar trend as with median percent change in seizure frequency; epileptic spasms (75%, n = 4) and atonic seizures (75%, n = 4) had the greatest responder rate, followed by tonic–clonic seizures (66.7%, n = 6), complex partial seizures (53.8%, n = 13), complex partial seizures with secondary generalization (50%, n = 4), and tonic seizures (42.9%, n = 7). The responder rate for total seizures after 3 months of treatment with CBD, however, is 50%. This, as well as responder rates at other time points, is summarized in Table 3.

Many TSC patients in this study also experienced seizure freedom from one or more of their seizure types. After 3 months of treatment with CBD, three patients (2, 9, and 16) were free of atypical absence seizures, three patients (9, 13, and 18) were free of tonic seizures, three patients (9, 10, and 15) were free of tonic–clonic seizures, two patients (9 and 15) were free of spasms, and two patients (3 and 9) were free of atonic seizures. Two patients (3 and 11) were nearly free of complex partial seizures, each with a percent change in complex partial seizures of −97%.

Clobazam levels as well as levels of its active metabolite, N-desmethylclobazam, may increase when CBD is administered, since cannabidiol and clobazam are both metabolized in the cytochrome P450 (CYP) pathway.[20] The responder rate after 3 months of treatment was 58.3% in patients taking clobazam concurrently (n = 12) and 33.3% in patients not taking clobazam (n = 6). The median percent change in seizure frequency after 3 months of treatment was −53.2% (IQR −69.1% to −8.9%) in patients taking clobazam concurrently, and −36.4% (IQR −63.1% to −19.6%) in patients not taking clobazam.

Seven patients (38%; nos 6, 8, 10, 11, 12, 15, and 18) experienced seizure aggravation at some time over the course of this study (Table 2). With the exception of patient 6, all patients whose total seizure frequency increased after starting CBD did so only within the first 6 months of treatment. Adjustment of CBD and concomitant AED doses as patients progressed through their 9th month of treatment, resulted in a decrease in total seizure frequency from baseline for nearly all study patients. Patient 6 experienced seizure aggravation starting after 9 months of treatment that continued into the 12th month, but has since been seizure-free after recent epilepsy surgery and continuing CBD treatment.

Depicted in Table 4, cognitive gains, including improved alertness, verbal communication, vocalizations, cognitive availability, and initiation of emotional and physical connections, were reported in 12 (85.7%) of 14 patients with physician- and parent-observed global developmental delays, and also in one patient who did not have any cognitive impairment at baseline. In addition, of the nine patients with physician- and parent-observed behavioral problems, behavioral improvements were reported in six (66.7%).

Table 3. Responder rates for seizure types

	2 Months (%)	3 Months (%)	6 Months (%)	9 Months (%)	12 Months (%)
Total	9/18 (50.0)	9/18 (50.0)	7/18 (38.9)	8/16 (50.0)	4/8 (50.0)
S	4/4 (100.0)	3/4 (75.0)	4/4 (100.0)	4/4 (100.0)	2/2 (100.0)
A	3/4 (75.0)	3/4 (75.0)	3/4 (75.0)	3/4 (75.0)	1/2 (50.0)
TC	3/6 (50.0)	4/6 (66.7)	3/6 (50.0)	3/5 (60.0)	1/1 (100.0)
CP	5/13 (38.5)	7/13 (53.8)	4/13 (30.8)	7/13 (53.8)	3/6 (50.0)
CP 2	1/4 (25.0)	2/4 (50.0)	2/4 (50.0)	2/3 (66.7)	1/2 (50.0)
T	4/7 (57.1)	3/7 (42.9)	4/7 (57.1)	4/6 (66.7)	1/2 (50.0)

S, spasms; A, atonic; TC, tonic–clonic; CP, complex partial; CP 2, complex partial with secondary generalization; T, tonic.
Responder rate is defined as the percent of patients who experienced a >50% reduction in seizure frequency. Data are presented as (number of responders)/(number of patients with seizure type x at time y), responder rate. Individual seizure types are listed in order of responder rate after 3 months of treatment.

Table 4. Dosing, adverse events, and cognition/behavior changes

Case no.	Maximum CBD dose	Current CBD dose	Time in study (months)	CBD-related adverse events	Cognitive gains	Behavior improved
1	50	50	22	None	No[a]	Yes
2	32	32	22	IR, DI	Yes[b]	Yes
3	25	21.4	17[c]	DR, DI	No[a]	NBD
4	50	50	14[c]	None	Yes[b]	NBD
5	50	50	22	None	Yes[b]	NBD
6	50	50	15	None	No	NBD
7	50	50	15	None	Yes	Yes
8	35	30	15	DR, AS, ATX, PS, AG	Yes	NBD
9	45	45	15	DR	Yes[a]	Yes
10	25	19	12[c]	DR	No[a]	NBD
11	15	13	11	DI, VM	No	Yes
12	45	40	9	DR, ATX	Yes[b]	NBD
13	40	40	11	AG	Yes	NBD
14	45	40	9	SS, DR, PS, ATX	Yes[b]	No
15	22	22	9	ATX, BD, DR	Yes	No
16	20	20	9	DI, DR, ATX, AG, CNF	Yes	Yes
17	40	40	7	IR	Yes[b]	NBD
18	40	40	7	None	No	No

IR, irritability; DI, diarrhea; DR, drowsiness; AS, appetite suppression; ATX, ataxia; PS, poor sleep; AG, agitation; VM, vomiting; SS, increased self-stimulation; BD, behavioral difficulties; CNF, confusion; NBD, no baseline behavioral difficulties.

[a]Patients without cognitive impairment (IQ $\geq$ 70) on initial neuropsychological testing. All other patients lack neuropsychological testing but still have physician- and parent-observed global developmental delays.

[b]Patients with cognitive impairment (IQ $<$ 70) on initial neuropsychological testing.

[c]Patients who exited the study.

With respect to seizures, both responders and nonresponders experienced cognitive and behavioral improvements during treatment with CBD.

As summarized in Table 4, over the course of this study, 15 (83%) of 18 total patients reached the initial maximum dose of 25 mg/kg/day of CBD, whereas 5 (27.8%) of 18 patients reached the study maximum of 50 mg/kg/day of CBD. All five of the patients who reached the maximum allowed dose of CBD experienced no CBD-related adverse events. Six (33.3%) of 18 patients decreased their CBD dose during the study either to optimize seizure control or to relieve adverse events and interactions with concomitant AEDs. The number of CBD-related adverse events experienced per patient ranges from 0 to 5, with a median of 1. Twelve (66.7%) of 18 patients in this study experienced at least one adverse event thought possibly related to CBD. Currently, 3 (16.7%) of 18 patients with TSC have exited the expanded access program; two patients stopped CBD treatment due to adverse events and one patient stopped CBD treatment due to seizure freedom. Patient 3 experienced diarrhea and weight loss and exited after 17 months; patient 4 had viral myocarditis unrelated to CBD and exited after 12 months. Patient 10 became seizure-free after epilepsy surgery and exited after 12 months. None of the TSC patients that stopped taking CBD did so due to lack of efficacy.

Most adverse events experienced in this study were temporary and of mild severity. Adverse events were resolved through dose adjustments of CBD or concomitant antiepileptic drugs. As described in Table 5, the most common adverse events were drowsiness (n = 8, 44.4%), ataxia (n = 5, 27.8%), and diarrhea (n = 4, 22.2%). No serious adverse events related to CBD were reported by TSC patients in this study.

Table 5. Frequency of CBD-related adverse events

Adverse event	Frequency (%)
Drowsiness	8 (44.4)
Ataxia	5 (27.8)
Diarrhea	4 (22.2)
Agitation	3 (16.7)
Poor sleep	2 (11.1)
Irritability	2 (11.1)
Appetite suppression	1 (5.6)
Confusion	1 (5.6)
Vomiting	1 (5.6)
Increased self-stimulation	1 (5.6)
Behavioral difficulties	1 (5.6)

Discussion

Under this expanded-access program for CBD as an adjunct treatment in patients with drug-resistant epilepsy, many patients with TSC exhibited an appreciable reduction in seizure frequency. After 3 months of treatment with CBD, the responder rate was 50%, with a median percent change in seizure frequency of −48.8%. In addition, the frequency of every seizure type experienced by patients in this study was reduced by at least 38.6%, with four of six different seizure types having a median percent decrease in

seizures over 50%. Although patients taking clobazam concurrently with CBD had a greater responder rate and median percent decrease in seizure frequency than patients not taking clobazam, there are few patients not taking clobazam and these results are likely not statistically significant. In addition, many patients continued to have well-controlled seizures after reducing their clobazam doses. In patients who experienced an increase in seizure frequency, dose adjustments while continuing CBD treatment alleviated seizure aggravation in nearly all cases. It is thought that the increased seizure frequency was a result of the natural history of each patient's epilepsy or due to a possible interaction between CBD and concomitant AEDs. Considering that all patients in this study are treatment resistant and have never had adequate seizure control—even after treatment with multiple antiepileptic drugs, dietary therapy, surgery, or VNS—CBD is a promising and effective treatment for seizures in patients with TSC.

Epileptic spasms present a great risk in the TSC population; spasms occur in approximately 38% of TSC patients and are strongly associated with the development of multiple seizure types, refractory epilepsy, and cognitive impairment.[4] The four TSC patients in this study with refractory epileptic spasms (8, 9, 13, and 15) had an age range of 3–31 years; all of these patients were taking clobazam and half were taking either levetiracetam, lacosamide, or valproic acid. After 3 months of treatment with CBD, the responder rate was 75%, the median percent change in spasm frequency was −87.5% (IQR −100% to −68.4%), and two of the four patients were spasm-free. In addition, after 6 months of treatment, the responder rate was 100% and the median percent change in spasm frequency was −96.2% (IQR −100% to −89.4%). Response to CBD with respect to spasms suggests that CBD is especially effective with this seizure type.

Reported cognitive and behavioral improvements during treatment with CBD are of great interest, given that approximately 50% of TSC patients have cognitive impairment and >50% of TSC patients have behavioral difficulties. Although patients in this study lacked a full follow-up neuropsychological evaluation after starting CBD, parents of patients reported cognitive gains in 85.7% of cases with baseline global developmental delays and behavioral improvements in 66.7% of cases with baseline behavioral problems. Surprisingly, behavioral and cognitive improvements were observed in both responders and nonresponders, indicating that CBD's positive effect on behavior and cognition may be somewhat independent of seizure control.

Adverse events thought possibly related to CBD, although mostly mild and temporary, were reported 12 (66.7%) of 18 TSC patients in this study; no serious CBD-related adverse events were reported. In addition, 5 (27.8%) of 18 TSC patients in this study titrated to the study maximum dose of 50 mg/kg/day with no adverse events, even though CBD was added to a median of three concomitant AEDs.

Most patients who were able to titrate up to 50 mg/kg/day were not taking clobazam concurrently; conversely, most patients who experienced adverse events and were not able to titrate up to the maximum dose were taking clobazam. CBD is known to inhibit the CYP2C19 and CYP3A4 enzymes that catalyze clobazam's active metabolite, N-desmethylclobazam, leading to side effects associated with clobazam, such as drowsiness, ataxia, and irritability.[20] Because these side effects were resolved by adjusting either CBD or clobazam dosing, they are thought to result from an interaction between CBD and clobazam. Diarrhea, another common adverse event observed in this study, is hypothesized to result from the ingestion of oil in the CBD solution rather than from CBD itself. Although all cases of diarrhea were alleviated by reducing CBD dose, and thus, the amount of oil ingested, it is unknown if diarrhea could be eased by administering the same dose of CBD in a more concentrated solution. However, considering the preceding, CBD is a relatively safe and well-tolerated treatment option.

One of the major limitations of this study is that the expanded access program is neither controlled nor double-blinded. Despite this, recent double-blind placebo-controlled studies for GWP42003-P in the treatment of Dravet syndrome have indicated a statistically significant median reduction in seizure frequency of 39% compared to a 13% reduction in seizure frequency for placebo[21]; this is comparable to seizure frequency reductions in controlled levetiracetam studies.[22,23] Parental reports of cognitive and behavioral changes also limit our results, since they are subjective.

Another limitation of our study is that the limited study size does not allow determination of statistical significance. In addition, doses of cannabidiol and concomitant AEDs were inconsistent between patients and across time. The combination of these factors makes it difficult to establish a strong correlation between dose, time, and response; especially so at later time points and less common seizure types where there are fewer data points.

Despite these limitations, these results suggest CBD's efficacy in reducing seizure activity in patients with TSC. To further characterize the role of CBD in the treatment of refractory epilepsy in TSC, randomized controlled trials are needed.

Acknowledgments

Thank you to GW Pharmaceuticals for providing the study drug and to the Herscot Center for Tuberous Sclerosis Complex for financial support.

Disclosure of Conflict of Interest

Elizabeth Thiele has served as a paid consultant for GW Pharmaceuticals. The remaining authors have no conflicts of interest. We confirm that

we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. *Lancet Neurol* 2015;14:733–745.
2. Henske EP, Jozwiak S, Kingswood JC, et al. Tuberous sclerosis complex. *Nat Rev Dis Primers* 2016;2:16035.
3. Chu-shore CJ, Major P, Camposano S, et al. The natural history of epilepsy in tuberous sclerosis complex. *Epilepsia* 2010;51:1236–1241.
4. Cilio MR, Thiele EA, Devinsky O. The case for assessing cannabidiol in epilepsy. *Epilepsia* 2014;55:787–790.
5. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 2014;55:791–802.
6. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol* 2015;15:270–278.
7. Francis FM. Cannabinoids for pediatric epilepsy? Up in smoke or real science? *Transl Pediatr* 2015;4:271–282.
8. Friedman D, Devinsky O. Cannabinoids in the treatment of epilepsy. *N Engl J Med* 2015;373:1048–1058.
9. Welty TE, Luebke A, Gidal BE. Cannabidiol: promise and pitfalls. *Epilepsy Curr* 2014;4:250–252.
10. Chesher GB, Jackson DM. Anticonvulsant effects of cannabinoids in mice: drug interactions within cannabinoids and cannabinoid interactions with phenytoin. *Psychopharmacologia* 1974;37:255–264.
11. Chesher GB, Jackson DM, Malor RM. Interaction of delta9-tetrahydrocannabinol and cannabidiol with phenobarbitone in protecting mice from electrically induced convulsions. *J Pharm Pharmacol* 1975;27:608–609.
12. Consroe PF, Wolkin AL. Anticonvulsant interaction of cannabidiol and ethosuximide in rats. *J Pharm Pharmacol* 1977;29:500–501.
13. Consroe P, Benedito MA, Leite JR, et al. Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice. *Eur J Pharmacol* 1982;83:293–298.
14. Izquierdo I, Tannhauser M. Letter: The effect of cannabidiol on maximal electroshock seizures in rats. *J Pharm Pharmacol* 1973;25:916–917.
15. Jones NA, Hill AJ, Smith I, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *J Pharmacol Exp Ther* 2010;332:569–577.
16. Jones NA, Glyn SE, Akiyama S, et al. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. *Seizure* 2012;21:344–352.
17. Turkanis SA, Smiley KA, Borys HK, et al. An electrophysiological analysis of the anticonvulsant action of cannabidiol on limbic seizures in conscious rats. *Epilepsia* 1979;20:351–363.
18. Cunha JM, Carlini EA, Pereira AE, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 1980;21:175–185.
19. Gloss D, Vickrey B. Cannabinoids for epilepsy. *Cochrane Database Syst Rev* 2012;6:CD009270.
20. Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia* 2015;56:1246–1251.
21. *GW pharmaceuticals announces positive phase 3 pivotal study results for epidiolex (cannabidiol)*. Cambridge, UK: GW Pharmaceuticals; 2016. Available at:http://www.gwpharm.com/GW%20Pharmaceuticals%20Announces%20Positive%20Phase%203%20Pivotal%20Study%20Results%20for%20Epidiolex%20cannabidiol.aspx. Accessed April 3, 2016.
22. Abou-Khalil BW. Levetiracetam in the treatment of epilepsy. *Neuropsychiatr Dis Treat* 2008;4:507–523.
23. Glauser TA, Ayala R, Elterman RD, et al. Double-blind placebo controlled trial of adjunctive levetiracetam in pediatric partial seizures. *Neurology* 2006;66:1654–1660.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Epilepsy treatment history.