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Original Article

Cannabidiol Treatment for Refractory Seizures in Sturge-Weber Syndrome

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ABSTRACT

BACKGROUND: Sturge-Weber syndrome results in leptomeningeal vascular malformations, medically refractory epilepsy, stroke(s), and cognitive impairments. Cannabidiol, a cannabinoid without psychoactive properties, has been demonstrated in preclinical models to possibly have anticonvulsant, antioxidant, and neuroprotective actions. **METHODS:** Five subjects with Sturge-Weber syndrome brain involvement and treatment-resistant epilepsy were enrolled. Motor seizure frequency, quality of life, and adverse events were recorded from the eighth week of the pretreatment period, eight weeks after starting maintenance dose (week 14), and the most recent visit. **RESULTS:** Four subjects had data through week 14, one of whom initially withdrew for lack of efficacy but because of other benefits re-enrolled with a lower dose. Two subjects at week 14 and three subjects with bilateral brain involvement had at the last visit a greater than 50% seizure reduction, reported an improved quality of life, and remained on cannabidiol 63-80 weeks after starting the drug. Three subjects reported mild side effects considered related to cannabidiol. **CONCLUSION:** This study suggests that cannabidiol may be well tolerated as adjunctive medication for seizure management and provides initial data supporting further study of cannabidiol in individuals with Sturge-Weber syndrome.

Keywords: Sturge-Weber syndrome, cannabidiol, intractable epilepsy, safety

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Introduction

Sturge-Weber syndrome (SWS) is a rare neurovascular disorder that results from a somatic R183Q mutation in *GNAQ*[1] leading to SWS skin involvement (port-wine birthmark [PWB] and associated complications of external tissue), eye involvement (glaucoma and vascular malformation of the eye), and brain involvement (leptomeningeal angioma and associated epilepsy, stroke, hemiparesis, and cognitive impairments).[2-5] Precisely how this mutation results in malformed blood vessels is the focus of current active research; however, it is likely that hyperactivation of the Ras-RAf-mitogen-activated protein kinases/extracellular signal-regulated kinases and mammalian target of rapamycin pathways contribute to abnormal vascular and brain tissue responses.[6] Epilepsy is common in SWS brain involvement, and a significant subset of these patients has medically refractory seizures. About 15% of patients with SWS have bilateral brain involvement, and for these patients in particular seizure control can be challenging, as most will not be good candidates for surgical resection.[7] Additional treatments are therefore needed, and this need served as the impetus of this study.

Compounds derived from the *Cannabis sativa* plant have received significant media attention for their potential to treat intractable seizures. Animal studies and anecdotal evidence suggest that cannabidiol (CBD) may have anticonvulsant effects. CBD binds only weakly to the CB_1 receptor, which may explain CBD's lack of psychotropic effects.[8] Several mechanisms by which CBD may have anticonvulsant effects

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have been proposed,[9] and because CBD is thought to block the mammalian target of rapamycin pathway and to have antioxidant and anti-inflammatory effects, it is of interest as a potential new treatment for SWS. CBD is being studied for stroke and hypoxic-ischemic injury as well.[10]

Although CBD has been studied for other pediatric epilepsies, most extensively for Dravet syndrome, Lennox-Gastaut syndrome, tuberous sclerosis, and febrile infection related epilepsy syndrome, SWS differs in that it is a neurovascular disorder; this may be important because CBD can have significant effects upon vascular reactivity.[11,12] Therefore it is important to study the safety of CBD for SWS in particular. We sought to begin to assess the safety and effectiveness of CBD for medically refractory seizures in SWS.

Materials and Methods

All participants had at least one clinical visit before consenting to this study, which was part of an expanded access program approved by the Federal Drug Administration for the use of Epidiolex© in the treatment of pediatric medically refractory epilepsy. This drug is a highly purified CBD derived from the cannabis plant and provided by GW Research. Findings reported in this study are specific to GW Research's formulation of CBD and cannot be extrapolated to other CBD products. The study protocol was approved by The Johns Hopkins Institutional Review Board and received an investigational new drug (IND) number from the Federal Drug Administration.

Protocol eligibility for this trial was determined and institutional review board approval obtained before identification or selection of any enrolled subjects, except for the following criteria that were changed to aid slow recruitment: (1) age was increased from 30 to 45 years (enrollment not impacted) and (2) the minimal frequency of seizures was decreased from three seizures per month to one per month for three months before recruitment and during the baseline period (this change impacted subject 5 and subject 3 [initial enrollment]). Other details on eligibility requirements are summarized in Table 1.

Previously enrolled participants who were required to withdraw for treatment failure before completing the study could be re-enrolled targeting a lower dose if they reported a decrease in seizures on the lower dose and other benefits. To be re-enrolled, previous participants had to wait at least four weeks after their final withdrawal visit and meet the remaining eligibility criteria. The ability to re-enroll was added to the protocol to re-enroll subject 3 at a lower dose, which she tolerated well and on which she demonstrated decreased seizures and other subjective benefits.

Visits took place at enrollment (week -8), at baseline (week 0), weekly during weeks one to six, and once each at weeks 10, 14, 20, 26, 38, and 48.

TABLE 1.
Eligibility and Exclusion Criteria

Eligibility Criteria:
Participants with Sturge-Weber syndrome brain involvement as defined on contrast enhanced magnetic resonance imaging (choroid plexus glomus, dilated deep draining vessels, and a leptomeningeal vascular malformation) and the following:

- Male or female, age one month to 45 years
- Documentation of a diagnosis of drug-resistant epilepsy as evidenced by failure to control seizures despite appropriate trial of two or more anticonvulsants at therapeutic doses. Drug-resistant epilepsy for this study is defined as: At least one reported quantifiable (no cluster or innumerable) defined seizure with motor signs per month for at least three months before initial visit and baseline visit
- One to five baseline antiepileptic drugs at stable doses for a minimum of four weeks before enrollment
- Vagus nerve stimulation therapy must be on stable settings for a minimum of three months before enrollment
- If on ketogenic or Atkins diet, must be on stable ratio for a minimum of three months before enrollment
- Previous subjects who failed at any point to meet continuation criteria and withdrew early may be considered for re-enrollment under a new subject ID as long as the above-mentioned inclusion criteria are met. The determination of whether to re-enroll can be made by the principal investigator and sponsor on a case-by-case basis. Re-enrollment can occur no earlier than four weeks after the final, postweaning follow-up visit under the old subject ID
- Written informed consent obtained from the patient or the patient's legal representative must be obtained before beginning treatment

Eligibility was determined at both the initial screening and consenting visit and at the baseline visit two months later
Exclusion Criteria:

- Patients with seizures secondary to metabolic, toxic, infectious, or psychogenic disorders, drug abuse, or acute medical illness
- Presence of only nonmotor partial seizures (without limb or facial movements, eye deviation, or head turning)
- Patients who require rescue medication during the baseline phase for more than six days
- Patients with any severe or uncontrolled medical conditions at randomization such as:
  a. liver disease, such as cirrhosis, decompensated liver disease, and chronic hepatitis (i.e., quantifiable hepatitis B virus DNA and/or positive HbsAg, quantifiable hepatitis C virus RNA)
  b. uncontrolled diabetes as defined by fasting serum glucose greater than 150 mg/dL
  c. active (acute or chronic) or uncontrolled severe infections
  d. patients with an active, bleeding diathesis
- Patients who have had a major surgery or significant traumatic injury within four weeks of study entry, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia), or patients who may require major surgery during the course of the study
- Patients who change the dose of the anticonvulsants during four weeks before screening or during the baseline period
- Prior treatment with any investigational drug within the preceding four weeks before study entry
- Patients with a history of noncompliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study. Those in foster care, unable to keep follow-up appointments, maintain close contact with the principal investigator or complete all necessary studies to maintain safety
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test

Treatment failure: defined as a less than 50% decrease in the average weekly number of motor seizures for at least four weeks, compared with the average weekly number of motor seizures during the eight-week baseline period. Treatment failure was first assessed 14 weeks after starting CBD (or 8 weeks after reaching steady state) and was reassessed at every visit thereafter

Data were also collected from vital signs, height and weight, physical examination, and a Sturge-Weber neurological score (neuroscore) completed by the principal investigator as previously described.[13]

The neuroscore is a Likert scale used to quantify clinical severity of seizure frequency, hemiparesis, presence or absence and severity of visual field cut, and cognitive function. Data were also collected from patient reports of medical history, prior and current anticonvulsant history, current concomitant and rescue medications, adverse events or side effects, and quality of life (QoL). For the QoL, subjects answered the question "Is your/your child's quality of life better or worse or not changed since your last visit?" A Likert scale of −3 to 3 (−3 = "A lot worse," −2 = "Moderately worse," −1 = "Mildly worse," 0 = "Not changed," 1 = "Mildly better," 2 = "Moderately better," and 3 = "A lot better") was used to evaluate changes in QoL over the course of the study.

Urine pregnancy tests were done for female participants who were approaching or had reached at least Tanner stage 2 (weeks -8, 0, 10, 14, 26, and 38). Blood was collected for concomitant anticonvulsant trough levels (weeks 0, 4, 6, 20, 14, 26, and 38), CBD blood levels (weeks 6 and 10), and complete blood count and chemistries (weeks 0, 4, 10, 14, 26, 38). Photographs of the facial PWB (if present) were taken at weeks 0, 6, 14, and 48 to score birthmark extent and severity.

Each participant began taking CBD (100 mg/mL) at a dose of 2 mg/kg/day in twice-daily doses. The dose was increased to 5 mg/kg/day at week 1 and by 5 mg/kg/day each subsequent week as tolerated up to a maximum dose of 25 mg/kg/day. Only two subjects were able to reach 25 mg/kg/day dosing because of side effects in the other three, and the maximum tolerated dose was only 20 mg/kg/day as these two had side effects on the highest dose.

All subjects were included in the statistical analyses except as described in the results. Statistics were run in IBM SPSS Statistics Version 23. Means and standard deviations were computed for age, anticonvulsant levels while on CBD, and CBD blood levels and metabolites (Table S3). Means were compared for seizure data using Student paired *t* tests, and percentage differences were also calculated. The Wilcoxon signed rank test was used to compare differences in the recorded SWS neuroscore and PWB score between visits.

Results

Demographics

Five patients (Table 2) were recruited (Caucasian, mean age 8 years, 10 months ± 6 years, 4 months, four female). Two participants dropped out because of lack of efficacy (week 38 and week 9). A third was withdrawn because of a temporary increase in seizures during dose titration but was later re-enrolled. Three subjects remain on the extension phase of the study and have been administered the study drug for greater than one year.

CBD doses

CBD doses attempted ranged from 5 to 25 mg/kg/day per the protocol titration. However, three subjects could not be titrated to 25 mg/kg/day because of side effects, and neither of the subjects who reached 25 mg/kg/day remained on this dose. Subjects experienced adverse side effects including sleepiness, behavioral issues, or increased seizures (see Table 3), and the dose of study drug was subsequently decreased. Drug dosage in the subject who initially withdrew because of an increase in seizures and later re-enrolled was increased only to 5 mg/kg/day because this was a dose that she tolerated well and on which she demonstrated a decrease in her seizures. No changes to either study drug or anticonvulsants were made because of measured levels. These data are noted in Tables S1 and S2 of the supporting information section.

TABLE 2.
Subject Demographics

Subject	Gender	Age at Enrollment (yrs.)	Brain Involvement	Skin Involvement	Eye Involvement	Concomitant Anticonvulsants at Enrollment	Previously Failed Anticonvulsants
Subject 1	Female	6	Left: small area of frontal parietal involvement, after prior focal surgical resection	None	None	Levetiracetam	Topiramate Valproic acid Carbamazepine Phenobarbital Lorazepam Clonazepam Lamotrigine
Subject 2	Female	7	Bilateral: frontal, parietal, occipital, and temporal lobe involvement	Bilateral	Left	Levetiracetam* Valproic acid† Felbamate† Clobazam†	Phenobarbital Lamotrigine Oxcarbazepine Rufinamide
Subject 3	Female	19	Bilateral: left hemispheric, right occipital, and right cerebellum involvement	Bilateral	Bilateral	Valproic acid Rufinamide Perampanel Clorazepate	Phenobarbital Phenytoin Lacosamide Topiramate Oxcarbazepine Clobazam Levetiracetam
Subject 4	Male	7	Bilateral: left hemispheric and bilateral brainstem and cerebellum involvement	Bilateral	Bilateral	Valproic acid Topiramate	Lacosamide Levetiracetam Oxcarbazepine
Subject 5	Female	2	Right: occipital, parietal, and posterior temporal lobe involvement	Right	Right	Oxcarbazepine Lacosamide	Levetiracetam Phenobarbital

* 20% increase in dose was made. However, this subject had previously been on much higher doses of levetiracetam (10 mL twice daily) without seizure control. Therefore, her full seizure control for the past year is not likely attributable to the increase to 7 mL twice daily.
† Discontinued this drug during the study.

TABLE 3.
Related Adverse Symptoms Reported by Subjects

Possibly Related Events	Subject IDs	Number of Subjects Experienced
Symptoms:		
Temporary increased seizures	Subject 1 Subject 2 (indirectly related) Subject 3*	3
Behavioral issues	Subject 4 Subject 5	2
Increased aspartate aminotransferase liver function test	Subject 2 (indirectly related)	1
†Right eye exotropia and redness/intermittent exotropia without redness	Subject 5	1
Tiredness	Subject 1	1

* Experienced during initial enrollment.
† Considered possibly related.

Side effects and adverse events

Table 3 shows adverse events reported that were possibly or probably due to CBD (see Table S2 for adverse events reported, but unlikely due to CBD). All subjects reported at least one adverse event related to CBD during the study. All events were transient and resolved either spontaneously or after dose changes in concomitant anticonvulsants or CBD. Only one subject had a change in concomitant anticonvulsants (see Table 2).

Seizures

Seizure frequency was significantly decreased both at the primary outcome time point and at the most recent visit in the four subjects who reached the primary outcome on study drug (paired two-tailed *t* test, Table 4). This finding was the same regardless of whether subject 3 was included (based on re-entry data) or excluded (based on initial withdrawal). A fifth subject was withdrawn for adverse events and lack of efficacy before the primary outcome time point (see Table 4) and if included in seizure analysis, significance is lost. No significant differences in rescue medication use were noted between baseline and time on CBD.

Quality of life

All subjects reported improvements in QoL for most of their time on CBD. All three subjects who have continued on CBD reported their QoL at last visit being "a lot better" since starting CBD.

Neuroscores, PWB scores, and other reported findings

Total neuroscores ranged from 6 to 11 (median: 10) for all five subjects at baseline. The four subjects who remained in the study through week 14 had total neuroscores of 10 or 11

TABLE 4.
Seizures for Each Subject

Subject	Motor Seizure Types Experienced	Ave. Number of Seizures per Month at Baseline	Ave. Number of Seizures per Month at Week 14	% Change in Seizure Frequency at Week 14 Compared With Baseline	Most Recent Visit on CBD	Ave. Number of Seizures per Month at Most Recent Visit on CBD	% Change in Seizure Frequency at Most Recent Visit on CBD Compared With Baseline	Current Status
Subject 1	Overall	33.5	30.0	**10% decrease**	Week 38	29.5	**12% decrease**	Removed from study for lack of efficacy
	Myoclonic	33.5	30.0	10% decrease		29.0	13% decrease	
	Simple partial	0	0			0.5	Increase	
Subject 2	Overall	3.0	0.5	**83% decrease**	Week 82	0	**100% decrease**	Remains on study drug
	Drop seizures	2.5	0	100% decrease		0	100% decrease	
	Simple partial	0.5	0	100% decrease		0	100% decrease	
	Complex partial	0	0.5	Increase		0		
Subject 3 **Initial**	Overall	1.5	0	Decrease	Week 5	4.0	133% increase	
	Simple partial	0	0			1.0	Increase	
	Complex partial	1.5	0	Decrease		3.0	100% increase	
Subject 3 **Re-enrolled**	Overall	3.0	2.0	**33% decrease**	Week 57	1.0	**83% decrease**	Remains on study drug
	Secondarily generalized	0.5	0	100% decrease		0	100% decrease	
	Simple partial	0	2.0	Increase		0.5	Increase	
	Complex partial	2.5	0	100% decrease		0.5	100% decrease	
Subject 4	Overall	5.0	0.5	**90% decrease**	Week 60	2.0	**64% decrease**	Remains on study drug
	Simple partial	1.0	0	100% decrease		0	100% decrease	
	Complex partial	4.0	0.5	88% decrease		2.0	50% decrease	
Subject 5	Complex partial (no other seizure types)	1.0	Not available	Not available	Week 6	2.0	100% increase	Removed from study for lack of efficacy

Abbreviations:
Ave. = Average
CBD = Cannabidiol
All values represent seizures within the 56 days before the listed visit.
Bold values indicate change in seizure frequency for subjects that completed through week 14.

at baseline. The Wilcoxon Signed Ranks test did not show statistical differences in the total neuroscore or subscores between baseline and week six, week 14, or the most recent visit on CBD. Parent report did not indicate changes to extent or severity of the birthmark, and scores were not significantly different between visits on the Wilcoxon Signed Ranks test. The following subjective improvements were reported: improvements in fine motor, gross motor, speech, and cognitive ability; improvements in weight gain, strength or balance, mobility, level of alertness, vocalization or communication, and mood and behavior; increased confidence and independence.

Discussion

The three subjects who responded best to CBD all had bilateral brain involvement, were given two or more anticonvulsants and low-dose aspirin at entry, and had significant cognitive, neurological, behavioral, or mood issues. They had all previously failed between two and seven other seizure medications. Other subjects failed to respond, however, and this pattern seems similar to the response noted in other disorders such as Dravet syndrome and Lennox-Gastaut syndrome.[9] The study is now in the extension phase, and the last follow-up for all current subjects has occurred after well past a year on CBD, suggesting that seizure control can be sustained in these participants.

At their most recent visit, the same three subjects reported QoL with subjective physical improvements, such as fine motor ability, and all reported some subjective cognitive benefit. Hemiparesis severity is often related to seizure severity in SWS. CBD and other cannabinoids are currently being studied for their effects on mood and cognition and for potential benefit in movement disorders.[14,15] Future studies should use quantitative measures such as neuropsychological testing and normed questionnaires to analyze cognition and behavior or a Purdue Pegboard test to measure motor changes.

Adverse events considered related to CBD were temporary and included behavioral issues, tiredness, temporary increase in seizures, and increased aspartate aminotransferase liver function test. The behavioral issues experienced by one subject at the highest dose (25 mg/kg/day) resolved upon decreasing the dose. Devinsky et al.[9] reported behavioral disturbance in five subjects (3.1%). Somnolence, fatigue, and lethargy were among the most commonly reported events by Devinsky et al., and related symptoms were transiently reported in four of five of the subjects with SWS in this study, although in only one case was the symptom considered related to CBD. In the other cases, these symptoms were related to other issues such as viral illness and were shared with family members. All subjects were taking low-dose aspirin at baseline and throughout the trial, and no issues were noted with increased bruising, nosebleeds, or gum bleeds. In addition, no strokes occurred.

One subject experienced a transient mild elevation of aspartate aminotransferase which returned to normal after discontinuation of valproic acid. The two other subjects who took concomitant valproic acid did not experience elevations of transaminase levels. Devinsky et al.[9] found that all subjects receiving CBD who experienced elevations in transaminase levels were taking concomitant valproic acid. This finding suggests an association, but the mechanism of this presumed interaction is unclear.

Epilepsy trials can be challenging in SWS because the syndrome is rare, and these patients often do not have large numbers of daily seizures. The three subjects who appear to have responded to CBD had initial seizure frequencies in the middle range of seizure frequency studied; the subject with the highest and the subject with the lowest initial seizure frequency did not respond. Although individuals with SWS often have fluctuating symptoms, the sustained improvement in the three subjects who responded was unexpected given the severity and refractory nature of their symptoms.

This study was limited by small sample size, a frequent limitation in work with rare diseases; it was difficult to recruit subjects who met the entry criteria for this study. In addition, the open-label (no placebo) design may have led to bias in parental and subject reporting of QoL and other subjective improvements. A larger number of subjects are needed to examine possible drug interactions. To enroll more subjects and include a placebo-controlled group, future studies of CBD in SWS will need to be multicentered.

In conclusion, more work is needed; however, the current understanding suggests CBD may be beneficial for the treatment of seizures and other symptoms in SWS. This study indicates that CBD may be safe to use in patients with SWS and warrants further study. These data highlight primary and secondary outcomes that can be targeted for further study and lay the foundation for future clinical trials.

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The most splendid achievement of all is the constant striving to surpass yourself and to be worthy of your own approval.

Denis Waitley

Appendix

TABLE S1.
Anticonvulsant Level Measurements at Baseline and Mean Measurements on Cannabidiol (CBD)

Anticonvulsant	Pre-CBD Level	Mean On-CBD Level	S.D. of Mean On-CBD Level
N = 3			
Valproic acid (mg/L)			
Subject 2	122	115	23
Subject 3	56	59	14
Subject 4	27	44	23
N = 2			
Levetiracetam (μg/mL)			
Subject 1	12.6	9.7	2.3
Subject 2	31.5	44.0	29.9
N = 1			
Clobazam—Subject 2 (ng/mL)	150	194	44
Clorazepate—Subject 3 (ng/mL)	54	128	51
Felbamate—Subject 2 (μg/mL)	47	42	19
Lacosamide—Subject 5 (μg/mL)	4	3	0.5
Oxcarbazepine—Subject 5 (μg/mL)	21	20.65	1.3
Perampanel—Subject 3 (ng/mL)	1000	928	58
Rufinamide—Subject 3 (μg/mL)	6.4	4.12	1.0
Topiramate—Subject 4 (μg/mL)	1.4	5.16	2.5

Subject 3 re-enrollment data only.

TABLE S2.
Unrelated Adverse Diagnoses and Symptoms Reported by Subjects

Unrelated Events	Number of Subjects Experienced
Diagnoses:	
Pneumonia (with hospitalization)	1
Upper respiratory infection	4
Otitis media	2
Flare-ups of seasonal, environmental allergies	2
Flu	1
Strep throat	1
Symptoms:	
Cough	3
Sleep problems	3
Sleep difficulties	1
Tiredness	2
Allergy symptoms	2
Sneezing, runny nose, watery eyes, redness under eyes	1
Sore throat, nasal congestion	1
Behavioral issues	3
Imitating stereotypy in others	1
General	1
Brief pseudoseizure	1
Decreased oral intake	2
Eye problems	2
Spasmus nutans	1
Pain	1
Fever	2
Headache/migraine	2
Vomiting	2
Bed-wetting	1
Carsickness	1
Diarrhea	1
Gastroparesis after placement of gastrostomy tube	1
Low hemoglobin/iron deficiency anemia	1
Menstrual cramps	1
Rash, swelling, limb pain, hives	1

TABLE S3.
Measured Levels of Cannabidiol (CBD) and Metabolites

Subject	Week on Study Drug	CBD Dose (mg/kg/day)	CBD Concentration (ng/mL)	6-OH-CBD Concentration (ng/mL)	7-OH-CBD Concentration (ng/mL)
CBD01	6	25	213	12.4	292 (ALQ >250)
	10	20	80.7	3.79	81.9
CBD02	6	10	56.8	3.57	37.8
	10	10	62.3	3.35	35.5
CBD03	6	5	60.5	2.06	26.2
	10	5	83.0	3.16	38.3
CBD04	6	25	124	6.17	46.0
	10	25	122	2.60	24.9
CBD05	6	5	19.4	BLQ	2.63

Abbreviation:
ALQ = Above limit of quantification
Batch acceptance criteria ranged from 20% to 25%.