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

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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 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 anti-epileptic 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 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 is 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 difficult-to-treat pediatric population.

Keywords

Epilepsy; Pediatric; Intractable; Cannabidiol; Side Effects; Medically refractory seizures; treatment-resistant

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Introduction

Childhood epilepsies beginning in the first few years of life are frequently characterized by seizures that are resistant to available treatments, including anti-epileptic drugs (AEDs), the ketogenic diet, high doses of steroids and surgery [1]. A high seizure burden in early childhood likely contributes to the severe cognitive, behavioral and motor delays common in these children [2].

When indicated treatments fail to control their child's seizures, some parents turn to alternative treatments. One of these alternative treatments is cannabidiol-enriched cannabis. The cannabis plant contains approximately 80 cannabinoids of which cannabidiol and Δ^9 -tetrahydrocannabinol (THC) are the two most abundant [3,4].

Cannabidiol and THC exert very different physiological effects. Most importantly, cannabidiol is not psychoactive. In recent years, medical uses of cannabis have focused on cannabidiol, both because of its non-psychoactive nature and because it shows promise in treating disease [5]. However, in states where medical cannabis is legal, cannabidiol is currently only available in whole plant preparations that contain all the components of the cannabis plant, including THC. This poses significant risks when administering cannabidiol-enriched cannabis to epileptic children. First, cannabis use during development has been correlated with deleterious effects on brain development and cognition, primarily due to THC [6,7]. Second, THC can be pro-convulsive in epileptic brains [8].

In contrast to THC, numerous studies conducted over the last 40 years demonstrate anticonvulsant effects of pure cannabidiol in partial and generalized seizure animal models, including acute and kindling models [9,10,11,12,13,14]. In humans, two small double blind, placebo-controlled studies examined pure cannabidiol in adults with treatment-resistant epilepsy. In 1978, Mechoulam et al. randomized nine patients to either 200mg/day of pure cannabidiol or placebo [15]. During the three-month trial, two of four patients treated with cannabidiol became seizure free, whereas seizure frequency was unchanged in the five patients receiving placebo. In a second small clinical trial, 15 adult patients suffering from treatment-resistant secondary generalized epilepsy were randomly divided to placebo or 400mg of pure cannabidiol daily for up to 18 weeks [16]. Among the eight cannabidiol patients, four had a marked reduction and three had a partial reduction in seizures. One of the seven patients on placebo experienced a partial reduction in seizures. The most often reported side effect of pure cannabidiol was drowsiness. No patients reported psychoactive effects. In contrast, an open-label study found that cannabidiol was ineffective in controlling seizures; Ames and Cridland reported that seizure frequency was unchanged in 12 institutionalized patients with uncontrolled seizures receiving 200 mg of pure cannabidiol daily [17].

With the legalization of medical cannabis in an increasing number of states, parents of children with uncontrolled seizures have opted to treat their children's seizures with cannabidiol-enriched cannabis. This trend has produced an online presence of parents describing cannabidiol-enriched cannabis use in children with epilepsy. We asked parents from a Facebook group to anonymously fill out a survey on their experience of giving

cannabidiol-enriched cannabis to their children in order to gain insights into current cannabidiol-enriched cannabis use as an alternative treatment for childhood epilepsy.

Methods

The Stanford University institutional review board judged the study exempt from requiring full review by the board. Study data were collected and managed using REDCap electronic data capture tools hosted at the Stanford Center for Clinical Informatics. REDCap (Research Electronic Data Capture) is a secure web-based application designed to support data capture for research studies [18]. The survey consisted of 24 questions that measured clinical factors, including diagnosis and seizure types, and the parental-reported effect of cannabidiol-enriched cannabis on the child's seizure frequency and side effects. The survey was presented to a Facebook group composed of approximately 150 parents supporting the use of cannabidiol-enriched cannabis to treat seizures in their children with treatment-resistant epilepsy. The survey link was posted and displayed for two weeks, then reposted to the top of the group's page for another two weeks. Twenty parents responded to the survey. Nineteen responses met the inclusion criteria – diagnosis of treatment-resistant epilepsy and cannabidiol-enriched cannabis use – and were included in the analysis. One response was excluded because the child's diagnosis did not include epilepsy.

Because the cannabidiol-enriched cannabis survey results had a large number of patients with Dravet Syndrome and reported mostly positive outcomes for both seizure control and side effects, we wanted to assess parents' response to the same survey questions with a well known and effective treatment for seizures in Dravet syndrome, stiripentol. This would allow us to see if the parents' responses to our seizure burden questions were similar to the results from a clinical trial of stiripentol. In addition, side effects across the two drugs could be compared. To this end, we administered the same survey substituting stiripentol in place of cannabidiol-enriched cannabis. The stiripentol survey was presented to a different Facebook support group composed of parents of children with Dravet Syndrome having approximately 800 members. The stiripentol survey link was also initially posted for two weeks, and reposted to the top of the group's page for two additional weeks. Twenty-two parents responded to the stiripentol survey and all responses were included in analysis. Responses from both surveys were descriptively analyzed.

Results

The results from the cannabidiol-enriched cannabis survey are summarized in Table 1. The children ranged in age from 2 to 16 years. Thirteen children had Dravet syndrome (one of whom had epilepsy in female with mental retardation, EMFR), four children had Doose syndrome, and one each had Lennox-Gastaut syndrome and idiopathic early-onset epilepsy. The children experienced a variety of seizure types including focal, tonic-clonic, myoclonic, atonic and infantile spasms. In all cases, except patient 14 (age 2 years), the children experienced treatment-resistant epilepsy for more than 3 years before trying cannabidiol-enriched cannabis. The 2 year old had experienced intractable seizures for 16 months before trying cannabidiol-enriched cannabis. The children had unsuccessfully tried an average of 12 other AEDs before their parents began cannabidiol-enriched cannabis treatment. The

doses of cannabidiol the parents reported providing ranged from less than 0.5 mg/kg/day to 28.6 mg/kg/day. The doses of THC contained within those samples were reported to range from 0 to 0.8mg/kg/day. To obtain dosage information, parents reported having their preparations tested at commercial medical cannabis testing facilities. Seizure frequency before administering cannabidiol-enriched cannabis ranged from 2 per week to 250 per day. The duration of cannabidiol-enriched cannabis administration ranged from two weeks to over one year. Sixteen (84%) of the 19 parents reported a reduction in their child's seizure frequency. Two parents reported that their child became seizure-free after more than 4 months of cannabidiol-enriched cannabis use. Of the remaining 14 parents reporting a change in seizure frequency, 8 reported a greater than 80% reduction in seizure frequency, three reported a greater than 50% seizure frequency reduction and three reported a greater than 25% seizure frequency reduction. Three parents reported no change. Twelve parents weaned their child from another AED after starting cannabidiol-enriched cannabis treatment (see Table 1).

Beneficial effects of cannabidiol-enriched cannabis other than reduced seizures included better mood (15/19, 79%), increased alertness (14/19, 74%), better sleep (13/19, 68%) and decreased self-stimulation (6/19, 32%). Negative side effects included drowsiness (7/19, 37%) and fatigue (3/19, 16%) (Table 2). Side effects reported while taking other AEDs included rash, vomiting, irritability, dizziness, confusion and aggressive behavior; none were reported with the use of cannabidiol-enriched cannabis.

To understand if our questions might produce results similar to clinical trial results, we asked for responses to an identical survey replacing cannabidiol-enriched cannabis with another AED in use for Dravet syndrome. We surveyed parents on a Facebook group about stiripentol, which is approved only in Europe (though Americans can obtain it). We asked these parents to report how stiripentol affects their child's seizure frequency as well as which side effects were evident on the drug. Fifteen of the 22 (68%) parents reported that stiripentol reduced their child's seizure frequency. Four parents reported a substantial increase in seizure frequency, while three parents reported no change. Common negative side effects reported on stiripentol included appetite decrease (5/22, 23%), weight loss (6/22, 27%), insomnia (4/22, 18%) and increased self-stimulation (3/22, 14%). The reports in response to our survey are consistent with published data on the effects of stiripentol in children with Dravet syndrome [19], and support that our survey questions identify seizure and side effects similar to clinical trial results.

Discussion

Summary

We found that parents of children with severe treatment-resistant epilepsies are using cannabidiol-enriched cannabis to treat their child's epilepsy. Parents report a high rate of success in reducing seizure frequency with this treatment. Cannabidiol-enriched cannabis appears to be behaviorally well tolerated with some positive side effects not commonly associated with other AEDs. There are, of course, multiple limitations of an anonymous parental survey. We cannot verify the doses or the children's response to the cannabidiol-enriched cannabis. We approached a group of parents who have an ongoing interest in using

cannabidiol-enriched cannabis for their children's seizures which likely selected for positive outcomes. Nonetheless, the overall positive results on seizure control in a medically refractory group of childhood epilepsies suggest further studies of cannabidiol are warranted.

Parents report reduced seizures

The report of reduced seizure burden in the population that we surveyed is surprising. The children comprised a highly refractory epilepsy population with the majority having Dravet syndrome, a severe form of childhood epilepsy that often does not respond to available treatments, including AEDs, the ketogenic diet and the vagus nerve stimulator [1]. The children had failed to respond to an average of 12 AEDs prior to the use of cannabidiol-enriched cannabis. The children experienced various seizure types and the parental reports suggest that cannabidiol-enriched cannabis may have efficacy for diverse seizures. The limited size of our survey and small representation of syndromes other than Dravet does not provide additional guidance on what epilepsy types to move forward with in clinical trials. It is important to note, however, that the diagnoses and seizure types reported in this anonymous survey could not be validated by an experienced clinician.

Parents report favorable side effects profile

Quality of life surveys show that adverse effects of AEDs have as much of an impact on the patient's ability to enjoy life as the seizures themselves [20]. Our survey reports that cannabidiol-enriched cannabis is behaviorally well tolerated and may have beneficial effects on cognition and mood. Many parents reported that their children experienced better sleep, increased alertness, and better mood while taking cannabidiol-enriched cannabis. These beneficial side effects are rarely reported with pediatric use of other AEDs [21]. Additionally, many negative side effects commonly associated with AEDs, such as irritability, insomnia and aggressive behavior were notably absent from the parent reports on cannabidiol-enriched cannabis. Because of the apparent efficacy of cannabidiol-enriched cannabis, 12 parents reported weaning their child from other AEDs, thereby further increasing the child's quality of life by removing negative side effects associated with those other AEDs.

Bias Issues

We recognize that this survey has multiple biases that prevent us from making strong conclusions about the overall efficacy of cannabidiol-enriched cannabis in pediatric epilepsy. The positive reports on seizure control and side effects prompted us to investigate whether the wording of the questions produced a strong positive bias. We conducted an additional survey, using the same questions, of parents using stiripentol, a drug that is approved for treatment of Dravet syndrome in Europe. Our results from the stiripentol survey are consistent with published studies on the efficacy and tolerability of stiripentol [19]. Because the answers to the stiripentol survey match the published data on stiripentol's effects, it is unlikely that the wording of the survey questions was inherently biased. Still, there remains the bias of subject selection, in that the parents involved in the Facebook group were proponents of using cannabidiol-enriched cannabis for their children.

Use of medical cannabis poses risks

The new trend of medical cannabis use in children poses risks due to a lack of standardization and regulation, imprecise dosing and possible adverse side effects and medication interactions. A lack of regulation and standardization in the medical cannabis industry results in products that are of questionable quality and composition. Most parents reported using cannabis extracts, either purchased from a dispensary, or directly from a medical cannabis grower. Cannabis extracts are often inaccurately labeled and can contain highly variable levels of cannabidiol and THC. These extracts could also contain contaminants, such as fungus and pesticides, which may cause long-term organ damage. Further, while published reports on pure cannabidiol in animal models, as well as in humans with epilepsy, have demonstrated an anticonvulsant effect of cannabidiol, the data on THC's role in epilepsy is conflicting. In some cases, THC has been shown to be pro-convulsive [22]. Furthermore, animal studies have demonstrated that removal of THC from epileptic animals treated with THC can lead to hyperexcitability [8,22].

Future Directions

Because parents are increasingly using artisanal preparations of cannabidiol-enriched cannabis in an attempt to reduce the child's seizure burden, it is critical to obtain more data about the safety and efficacy of cannabidiol. These poorly regulated preparations may not represent the potential benefits and risks of pure cannabidiol. Formal studies to determine safety, optimal dosing, tolerability and efficacy of a standardized cannabidiol preparation in different populations of children and adults with epilepsy will provide the data necessary to determine whether cannabidiol has a place in epilepsy treatment.

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Table 1

Summary of Survey Responses

Patient	Diagnosis	Age & Sex	Age at Seizure Onset	Time on CBD	CBD (mg/kg/day)	THC (mg/kg/day)	Seizures before CBD	Seizures after CBD	Estimated Change in Seizure Frequency	Number of AEDs tried before CBD	AEDs discontinued while on CBD
1	LGS	7y female	<1y	> 1y	?	?	> 100/day	8-10/day	> -80%	8	Banzel, Onfi
2	DS	14y female	<1y	> 4m	14	0.5	5/day	0-1/day	> -80%	12	
3	EMFR	12y female	<1y	2-4m	7	0.5	12/day	0-1/day	> -80%	17	
4	DS	7y male	<1y	> 4m	8	0.25-0.5	50/week	50/week	0	16	
5	DS	6y female	<1y	> 4m	4	0.1-0.25	200-300/week	0-2/week	> -80%	6	Onfi
6	DS	16y female	<1y	> 4m	1-2	0.02-0.1	7/week	4/week	-25%	16	Onfi
7	DS	13y male	<1y	3-4m	4	0.02-0.1	40/week	30/week	-25%	16	Phenobarbital, Depakote
8	DS		<1y	> 4m	?	?	3/week	1-2/week	-50%	14	Klonopin
9	DS	male	<1y	> 4m	3-4	0.04-0.2	100-500/week	1-2/week	> -80%	10	STP, Topamax, Depakote
10	DS		<1y	> 4m	4	0.2-0.4	200-300/week	20-50/week	> -80%	12	STP

Patient	Diagnosis	Age & Sex	Age at Seizure Onset	Time on CBD	CBD (mg/kg/day)	THC (mg/kg/day)	Seizures before CBD	Seizures after CBD	Estimated Change in Seizure Frequency	Number of AEDs tried before CBD	AEDs discontinued while on CBD
11	DS	8y female	<1y	> 1y	?	?	5-10/week	0-3/week	-60%	10	STP, Onfi, Depakote
12	DS	7y female	<1y	> 4m	3-4	0.04-0.2	20+/week	0-10/week	-50%	10	Onfi, Zonisamide, Depakote
13	Doose	9y female	<1y	> 4m	10-13	0.5	60-250/day	0	> -80%	15	Lorazepam, Ethosuximide
14	DS	2y male	<1y	> 4m	7	0.08-0.4	2/week	0	> -80%	4	
15	Doose		2-5y	2w	<0.5	0.01-0.05	1-7/week	1-7/week	0	13	
16	Doose	11y male	2-5y	1-2m	6	0.6-0.8	20/week	4/week	> -80%	13	
17	Doose		2-5y	1-2m	6	0	15-20/day	0-3/day	> -80%	14	Steroids
18	Idiopathic	female	1-2y	< 1m	28	0.5-0.7	10/week	8/week	-25%	5	Valproic Acid
19	DS	6y female	<1y	> 4m	1	0.06-0.3	3/week	3/week	0	?	

LGS, Lennox-Gastaut syndrome; DS, Dravet syndrome, EMFR, Epilepsy in females with mental retardation; STP, Stiripentol; y, year; m, month.

Table 2
Reported side effects

	Cannabidiol	Stiripentol	All AEDs
Positive Side Effects			
Better Mood	15/19 (79%)	6/22 (27%)	4/22 (18%)
Increased Alertness	14/19 (74%)	5/22 (23%)	6/22 (27%)
Better Sleep	13/19 (68%)	6/22 (27%)	5/22 (23%)
Decreased Self-stimulation	6/19 (32%)	2/22 (9%)	3/22 (14%)
Negative Side Effects			
Drowsiness	7/19 (37%)	5/22 (23%)	20/22 (91%)
Fatigue	3/19 (16%)	7/22 (32%)	19/22 (86%)
Appetite Decrease	1/19 (5%)	5/22 (23%)	17/22 (77%)
Irritability	--	2/22 (9%)	17/22 (77%)
Insomnia	--	4/22 (18%)	17/22 (77%)
Aggressive Behavior	--	1/22 (5%)	15/22 (68%)
Weight Loss	--	6/22 (27%)	15/22 (68%)
Increased Self-stimulation	--	3/22 (14%)	14/22 (64%)
Appetite Increase	--	2/22 (9%)	10/22 (45%)
Confusion	--	--	9/22 (41%)
Weight Gain	--	1/22 (5%)	9/22 (41%)
Anxiety	--	1/22 (5%)	7/22 (32%)
Nausea	--	2/22 (9%)	6/22 (27%)
Rash	--	--	5/22 (23%)
Vomiting	--	2/22 (9%)	5/22 (23%)
Dizziness	--	--	5/22 (23%)

--, not reported