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Brief Communication

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 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.

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1. Introduction

Childhood epilepsies beginning in the first few years of life are frequently characterized by seizures that are resistant to available treatments, including antiepileptic drugs (AEDs), 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 nonpsychoactive 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 children with epilepsy. 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 proconvulsive in epileptic brains [8,23].

In contrast to THC, numerous studies conducted over the last 40 years demonstrate the anticonvulsant effects of pure cannabidiol in partial and generalized seizure animal models, including acute and kindling models [9–14]. In humans, two small double-blind, placebo-controlled studies examined pure cannabidiol in adults with treatment-resistant epilepsy. In 1978, Mechoulam and Carlini randomized nine patients to either 200 mg/day of pure cannabidiol or a 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 into a group that received placebo and a group that received 400 mg of pure cannabidiol daily for up to 18 weeks [16]. Among the eight patients treated with cannabidiol, four had a marked reduction, and three had a partial reduction in seizures. One of the seven patients receiving placebo experienced a partial

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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, some 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 the current use of cannabidiol-enriched cannabis as an alternative treatment for childhood epilepsy.

2. 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 Research Electronic Data Capture (REDCap) tools hosted at the Stanford Center for Clinical Informatics. Research Electronic Data Capture (REDCap) 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 the analysis. Responses from both surveys were descriptively analyzed.

3. 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 (EFMR)), 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 patient 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 dosages of cannabidiol the parents reported to be providing their children ranged from less than 0.5 mg/kg/day to 28.6 mg/kg/day. The dosages of THC contained within those samples were reported to range from 0 to 0.8 mg/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% reduction in seizure frequency, and three reported a greater than 25% reduction in seizure frequency. Three parents reported no change. Twelve parents weaned their child from another AED after starting cannabidiol-enriched cannabis treatment (see Table 1).

The parent-reported 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). The side effects reported while taking other AEDs included rash, vomiting, irritability, dizziness, confusion, and aggressive behavior; none of these 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 the published data on the effects of stiripentol in children with Dravet syndrome [19] and support the idea that our survey questions identify seizure and side effects similar to the clinical trial results.

4. Discussion

4.1. Summary

We found that some 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 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 group of patients with medically refractory childhood epilepsies suggest that further studies of cannabidiol are warranted.

Table 1
Summary of survey responses.

Patient	Diagnosis	Age and 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	7 y, female	<1 y	>1 y	?	?	>100/day	8–10/day	>−80%	8	Banzel, Onfi
2	DS	14 y, female	<1 y	>4 m	14	0.5	5/day	0–1/day	>−80%	12	
3	EFMR	12 y, female	<1 y	2–4 m	7	0.5	12/day	0–1/day	>−80%	17	
4	DS	7 y, male	<1 y	>4 m	8	0.25−0.5	50/week	50/week	0	16	
5	DS	6 y, female	<1 y	>4 m	4	0.1–0.25	200–300/week	0–2/week	>−80%	6	Onfi
6	DS	16 y, female	<1 y	>4 m	1–2	0.02–0.1	7/week	4/week	−25%	16	Onfi
7	DS	13 y, male	<1 y	3–4 m	4	0.02–0.1	40/week	30/week	−25%	16	Phenobarbital, Depakote
8	DS		<1 y	>4 m	?	?	3/week	1–2/week	−50%	14	Klonopin
9	DS	Male	<1 y	>4 m	3–4	0.04–0.2	100–500/week	1–2/week	>−80%	10	STP, Topamax, Depakote
10	DS		<1 y	>4 m	4	0.2–0.4	200–300/week	20–50/week	>−80%	12	STP
11	DS	8 y, female	<1 y	>1 y	?	?	5–10/week	0–3/week	−60%	10	STP, Onfi, Depakote
12	DS	7 y, female	<1 y	>4 m	3–4	0.04–0.2	20+/week	0–10/week	−50%	10	Onfi, Zonegran, Depakote
13	Doose	9 y, female	<1 y	>4 m	10–13	0.5	60–250/day	0	>−80%	15	Lorazepam, ethosuximide
14	DS	2 y, male	<1 y	>4 m	7	0.08–0.4	2/week	0	>−80%	4	
15	Doose		2–5 y	2 w	<0.5	0.01–0.05	1–7/week	1–7/week	0	13	
16	Doose	11 y, male	2–5 y	1–2 m	6	0.6–0.8	20/week	4/week	>−80%	13	
17	Doose		2–5 y	1–2 m	6	0	15–20/day	0–3/day	>−80%	14	Steroids
18	Idiopathic	Female	1–2 y	<1 m	28	0.5–0.7	10/week	8/week	−25%	5	Valproic acid
19	DS	6 y, female	<1 y	>4 m	1	0.06–0.3	3/week	3/week	0	?	

LGS, Lennox–Gastaut syndrome; DS, Dravet syndrome; EFMR, epilepsy in females with mental retardation; STP, stiripentol; y, year/years; m, month/months; w, weeks.

4.2. Parents report reduced seizures

The report of reduced seizure burden in the population that we surveyed is surprising. The children comprised a population with highly refractory epilepsy with the majority having Dravet syndrome, a severe form of childhood epilepsy that often does not respond to available treatments, including AEDs, ketogenic diet, and vagus nerve stimulation [1]. The seizures in children had failed to improve with 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 the small representation of syndromes other than Dravet do 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.

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.

4.3. Parents report favorable side effect profiles

Quality-of-life surveys show that the 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 suggest 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 the negative side effects associated with those other AEDs.

4.4. 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 the 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.

4.5. Use of medical cannabis poses risks

The new trend of medical cannabis use in children poses risks because of 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, purchased either 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 are conflicting. In some cases, THC has been shown to be proconvulsant [22]. Furthermore, animal studies have demonstrated that the removal of THC from epileptic animals treated with THC can lead to hyperexcitability [8,22].

4.6. Future directions

Because parents are increasingly using artisanal preparations of cannabidiol-enriched cannabis in an attempt to reduce their 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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Note from the Editor: Publication of this paper does not imply approval or endorsement of providing or administering cannabidiol-enriched cannabis to children for the treatment of epilepsy.

References

[1] Wheless JW. Managing severe epilepsy syndromes of early childhood. J Child Neurol 2009;24:24S–32S [quiz 33S-26S].
[2] McTague A, Cross JH. Treatment of epileptic encephalopathies. CNS Drugs 2013;27:175–84.
[3] Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. Science 1970;169:611–2.
[4] Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci 2009;30:515–27.
[5] Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. Rev Bras Psiquiatr 2008;30:271–80.
[6] Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A 2012;109:E2657–64.
[7] D'Souza DC, Sewell RA, Ranganathan M. Cannabis and psychosis/schizophrenia: human studies. Eur Arch Psychiatry Clin Neurosci 2009;259:413–31.
[8] Karler R, Turkanis SA. Subacute cannabinoid treatment: anticonvulsant activity and withdrawal excitability in mice. Br J Pharmacol 1980;68:479–84.
[9] Izquierdo I, Orsingher OA, Berardi AC. Effect of cannabidiol and of other cannabis sativa compounds on hippocampal seizure discharges. Psychopharmacologia 1973;28:95–102.
[10] Izquierdo I, Tannhauser M. Letter: the effect of cannabidiol on maximal electroshock seizures in rats. J Pharm Pharmacol 1973;25:916–7.
[11] Cox B, ten Ham M, Loskota WJ, Lomax P. The anticonvulsant activity of cannabinoids in seizure sensitive gerbils. Proc West Pharmacol Soc 1975;18:154–7.
[12] Consroe P, Benedito MA, Leite JR, Carlini EA, Mechoulam R. Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice. Eur J Pharmacol 1982;83:293–8.
[13] Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, Whalley BJ, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. J Pharmacol Exp Ther 2010;332:569–77.
[14] Jones NA, Glyn SE, Akiyama S, Hill TD, Hill AJ, Weston SE, et al. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. Seizure 2012;21:344–52.
[15] Mechoulam R, Carlini EA. Toward drugs derived from cannabis. Die Naturwissenschaften 1978;65:174–9.
[16] Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology 1980;21:175–85.
[17] Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. S Afr Med J 1986; 69:14.
[18] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
[19] Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet 2000;356:1638–42.
[20] Wheless JW. Intractable epilepsy: a survey of patients and caregivers. Epilepsy Behav 2006;8:756–64.
[21] Bourgeois BF. Initiating antiepileptic drug treatment and characteristics of drugs. Handb Clin Neurol 2013;111:719–25.
[22] Consroe P, Martin P, Eisenstein D. Anticonvulsant drug antagonism of delta9tetrahydrocannabinol-induced seizures in rabbits. Res Commun Chem Pathol Pharmacol 1977;16:1–13.
[23] Turkanis SA, Karler R. Excitatory and depressant effects of delta 9-tetrahydrocannabinol and cannabidiol on cortical evoked responses in the conscious rat. Psychopharmacology 1981;75:294–8.