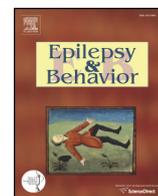




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Brief Communication

Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox–Gastaut syndrome

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ABSTRACT

There is a great need for safe and effective therapies for treatment of infantile spasms (IS) and Lennox–Gastaut syndrome (LGS). Based on anecdotal reports and limited experience in an open-label trial, cannabidiol (CBD) has received tremendous attention as a potential treatment for pediatric epilepsy, especially Dravet syndrome. However, there is scant evidence of specific utility for treatment of IS and LGS. We sought to document the experiences of children with IS and/or LGS who have been treated with CBD-enriched cannabis preparations. We conducted a brief online survey of parents who administered CBD-enriched cannabis preparations for the treatment of their children's epilepsy. We specifically recruited parents of children with IS and LGS and focused on perceived efficacy, dosage, and tolerability. Survey respondents included 117 parents of children with epilepsy (including 53 with IS or LGS) who had administered CBD products to their children. Perceived efficacy and tolerability were similar across etiologic subgroups. Eighty-five percent of all parents reported a reduction in seizure frequency, and 14% reported complete seizure freedom. Epilepsy was characterized as highly refractory with median latency from epilepsy onset to CBD initiation of five years, during which the patient's seizures failed to improve after a median of eight antiseizure medication trials. The median duration and the median dosage of CBD exposure were 6.8 months and 4.3 mg/kg/day, respectively. Reported side effects were far less common during CBD exposure, with the exception of increased appetite (30%). A high proportion of respondents reported improvement in sleep (53%), alertness (71%), and mood (63%) during CBD therapy. Although this study suggests a potential role for CBD in the treatment of refractory childhood epilepsy including IS and LGS, it does not represent compelling evidence of efficacy or safety. From a methodological standpoint, this study is extraordinarily vulnerable to participation bias and limited by lack of blinded outcome ascertainment. Appropriately controlled clinical trials are essential to establish efficacy and safety.

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1. Introduction

There is a great need for safe and effective therapies in the management of refractory childhood epilepsy, especially in the context of potentially devastating epileptic encephalopathies such as infantile spasms (IS) and Lennox–Gastaut syndrome (LGS) [1]. Despite rather limited preclinical and epidemiologic evidence and a lack of well-designed clinical trials, cannabidiol (CBD)—as well as CBD-enriched whole plant (*Cannabis sativa*) extracts—has generated enormous interest as a potential treatment for epilepsy [2], most notably in the setting of Dravet syndrome (severe myoclonic epilepsy of infancy, SMEI) [3]. This has occurred amidst widespread media reports extolling the virtue of CBD-enriched cannabis preparations and numerous online

testimonials from parents who have administered these products to their children [4]. Online forums are replete with seemingly miraculous responses to CBD after the failure of numerous mainstream medical and surgical therapies. Of note, there is significant debate as to the relative potential value of CBD-enriched whole plant extracts [5] (which include numerous other phytocannabinoids, terpenes, and other marijuana constituents which may exert effects on the central nervous system) versus purified or synthetic preparations [6] of CBD. Clinical trials of multiple cannabidiol preparations are eagerly anticipated.

In a recent internet-based survey conducted by Porter and Jacobson, 84% of parents who had administered CBD-enriched cannabinoid products to 17 children with epilepsy (including 13 with SMEI) reported substantial reductions in seizure frequency [7]. The aim of this study was to follow up on this early report of community use by extending a similar questionnaire to a larger cohort and by expanding the focus to other types of highly refractory childhood epilepsy, namely, IS and LGS. At the outset, we acknowledged that a survey—especially one

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administered online—is vulnerable to multiple potential confounds and may foster misleading conclusions. Nonetheless, given the attendant dangers and widespread use of CBD products, often without physician supervision or consent, the epilepsy community must attempt to reconcile the often disparate views of practitioners and patients (parents) [8].

2. Methods

2.1. Standard protocol approvals

This use of human subjects and the analyses presented here were approved by the Institutional Review Board at UCLA. The requirement for written informed consent was waived.

2.2. Survey design and administration

We designed a brief and streamlined survey to ascertain basic parental impressions of efficacy and side effects and to stratify these views according to epilepsy syndromes. The study was advertised in multiple online forums including the Infantile Spasms Community (www.IScommunity.org) and the Lennox–Gastaut Foundation (www.LGSfoundation.org). The survey was conducted using the infrastructure of SurveyMonkey (www.SurveyMonkey.com) and required respondents to (1) indicate consent to participate in the study, (2) verify that they are the parent or guardian of a child with epilepsy, and (3) confirm that their child received a cannabinoid product. We specifically did not collect data intended to identify patients. Respondents proceeded through a series of questions regarding epilepsy syndrome classification, underlying etiology, semiquantitative impression of efficacy, incidence of side effects before and after CBD exposure, and extent of CBD exposure (duration and dosage). The number of questions was minimized to reduce mid-study dropout. Several measures were undertaken to prevent fraudulent responses including the screening of IP addresses to preclude multiple responses from a single individual and the systematic review of data to identify responses of questionable authenticity.

2.3. Statistical methods

Continuous summary data were presented as median and interquartile range (IQR) based on nonparametric distributions where appropriate. Unpaired comparisons of proportions, paired comparisons of proportions, unpaired comparisons of medians, and paired comparisons of medians were carried out using the Fisher exact (FE), McNemar, Wilcoxon rank-sum (WRS), Wilcoxon signed-rank (WSR) tests, respectively. The Bonferroni method was used to adjust for multiple comparisons. Calculations were accomplished using STATA software (version 11, Statcorp, College Station, Texas, USA).

3. Results

3.1. Respondents

Between August 8 and August 24, 2014, there were 200 unique responses to our survey invitation. We excluded one respondent who did not consent to participate, 21 respondents who were not the parent or caregiver of a child with epilepsy, and 61 respondents whose children had not received a CBD product. Accordingly, the analyses presented here are based on the remaining 117 respondents. The median time required to complete the survey was 11.0 min (IQR = 7.1–16.4).

3.2. Patient demographics

Attributes of the study population and characteristics of CBD product exposure are summarized in Table 1. As intended, our study cohort was enriched with patients suffering from epileptic encephalopathy. Our

Table 1
Characteristics of the study population and CBD exposure.

<i>Patient demographics (n = 117)</i>	
Age at epilepsy onset, months ^a	5.5 (3.0–24.0)
Age at CBD treatment, years ^a	6.0 (3.0–10.0)
Latency from epilepsy onset to CBD initiation, years ^a	5.0 (2.3–9.0)
Number of failed medications prior to CBD exposure ^a	8.0 (4.0–12.0)
Failed ketogenic diet therapy before CBD exposure, n (%)	53 (45.3)
Failed resective surgery before CBD initiation, n (%)	13 (11.1)
Failed vagal nerve stimulation before CBD exposure, n (%)	21 (17.9)
<i>Epilepsy syndrome^b</i>	
Infantile spasms, n (%)	45 (38.5)
Lennox–Gastaut syndrome, n (%)	24 (20.5)
Infantile spasms and/or Lennox–Gastaut syndrome, n (%)	53 (45.2)
Severe myoclonic epilepsy of infancy (SMEI, Dravet syndrome), n (%)	15 (12.8)
Myoclonic–astatic epilepsy (MAE, Doose syndrome), n (%)	5 (4.3)
Other/unknown, n (%)	44 (37.6)
<i>CBD exposure^c</i>	
Duration of CBD treatment, months ^a	6.8 (3.8–9.8)
Continued CBD treatment at the time of survey completion, % (n = 101)	93.1
CBD product with at least 15:1 ratio of CBD to THC, % (n = 91)	83.5
CBD dosage, mg/kg/day ^a (n = 46)	4.3 (2.9–7.5)
Number of medications continued during CBD exposure ^a (n = 117)	2.0 (0.0–3.0)

^a Median, interquartile range.

^b Infantile spasms and Lennox–Gastaut syndrome were coexistent in most cases. There was no overlap between SMEI and infantile spasms or Lennox–Gastaut syndrome. IS and/or LGS, SMEI, MAE, and other sum to 100%.

^c Many patients were not able to provide detailed information regarding CBD exposure. Reported percentages are based on a subset of respondents.

questionnaire did not adequately distinguish between patients with IS and patients with LGS, and many patients appeared to have met diagnostic criteria for both disorders. Patients with IS and LGS were pooled in the stratified analyses that follow. Whereas the median age at epilepsy onset was 5.5 months, CBD exposure typically followed years of highly intractable epilepsy, with the children's seizures having failed to improve after a median of eight antiseizure drug trials, as well as frequent failure of the ketogenic diet therapy (45.3%), resective surgery (11.1%), and vagal nerve stimulation (17.9%). Although the youngest child in this study was 5 months old at CBD initiation, children tended to be much older at first exposure (IQR = 3 to 10 years).

The vast majority of respondents reported using CBD-enriched oil-based extracts, which were typically administered 2–3 times a day. Of parents who knew the CBD-to-tetrahydrocannabinol (THC) ratio, a great majority reported ratios of at least 15:1. Only a minority of parents were able to provide specific CBD dosages (i.e., mg CBD per day). Among 46 parents who reported patient weight and daily dosage, the median weight-based dosage of CBD was 4.3 mg/kg/day (IQR = 2.9–7.5). The median duration of CBD exposure was 6.8 months (IQR = 3.8–9.8).

3.3. Perceived efficacy

As illustrated in Fig. 1, respondents reported dramatic subjective efficacy of CBD. Although five respondents reported an increase in seizure frequency and 11 reported no change, 100 (85%) reported a reduction in seizure frequency, including 16 (14%) reporting complete seizure freedom. One respondent did not answer the question regarding efficacy. Perceived changes in seizure frequency were typically observed quickly: 86% reported improvement or worsening within 14 days. Response patterns were similar across parent-identified epilepsy syndromes.

In an underpowered, exploratory analysis using only those subjects for whom dosage data were available, we did not observe a significant difference in median dosage between children with (4.3, IQR = 2.4–7.0) and children without (6.0, IQR = 3.9–9.2) a reduction in seizures ($p = 0.27$, WRS) or among responders who were (7.4, IQR = 3.8–19.1) or were not (4.2, IQR = 2.3–6.8) seizure-free ($p = 0.16$, WRS). We further investigated whether response (reduction in seizure frequency or seizure freedom) was associated

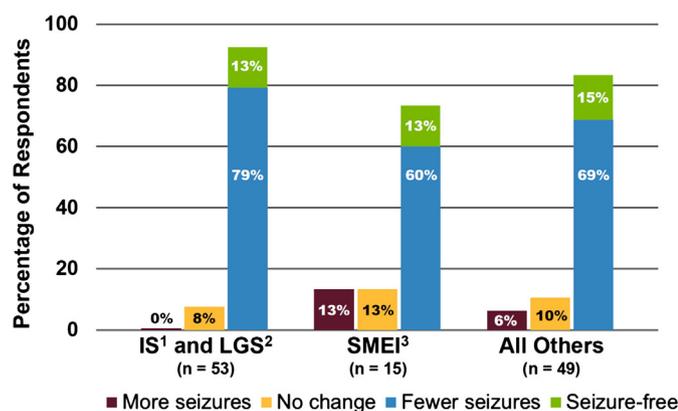


Fig. 1. Perceived response to CBD exposure. ¹Infantile spasms. ²Lennox–Gastaut syndrome. ³Severe myoclonic epilepsy of infancy (Dravet syndrome).

with coadministration of specific antiseizure drugs. Although response was not positively correlated with the concomitant use of any antiseizure drug, the ketogenic diet, or ongoing vagal nerve stimulation, coadministration of phenytoin use was associated with lack of response ($p < 0.001$, McNemar) and remained significant after Bonferroni correction for multiple comparisons. This likely reflects the observation that phenytoin may exacerbate epileptic encephalopathies including SMEI [9,10] and, as a CYP 3A4/2C19 inducer, may reduce plasma levels of cannabidiol, a likely 3A4/2C19 substrate [11]. Conversely, some perceived efficacy of CBD may instead represent CBD-mediated CYP2C19 inhibition, leading to higher serum levels of N-desmethyloclobazam, and thus efficacy better attributed to clobazam or other antiseizure drugs. However, in an underpowered analysis, we did not detect an association between response to CBD and concomitant clobazam administration.

3.4. Perceived side effects and tolerability

Reported side effects before and during CBD exposure are summarized in Table 2. With respect to tolerability, the median number of side effects reported during CBD exposure (1, IQR = 0–2) was far lower than reported before CBD exposure (5, IQR = 2–10). While this comparison was statistically significant ($p < 0.001$, WSR), the validity of the comparison is diminished by the observation that children had a much greater opportunity to suffer any side effect before CBD exposure; the median latency from epilepsy onset to CBD initiation

Table 2

Perceived side effects before CBD exposure and during CBD exposure.

Side effect	Before CBD	During CBD
Fatigue, %	70.1	9.4
Drowsiness, %	70.9	12.8
Nausea, %	35.9	6.8
Vomiting, %	23.9	2.6
Rash, %	10.3	0.0
Increased appetite, %	12.8	29.9
Decreased appetite, %	40.2	6.0
Weight loss, %	35.0	4.3
Weight gain, %	17.9	29.1
Irritability, %	59.0	9.4
Dizziness, %	35.9	0.0
Anxiety, %	35.9	3.4
Insomnia, %	43.6	5.1
Confusion, %	35.0	0.9
Obsessive behavior, %	23.9	2.6
Aggressive behavior, %	40.2	4.3
Total number of adverse effects reported ^a	5 (2–10)	1 (0–2)

^a Median, interquartile range.

(60.0 months, IQR = 28.0–108.0) was far longer than the median duration of CBD exposure (6.8 months, IQR = 3.8–9.8), with $p < 0.001$ (WSR). Furthermore, fewer side effects reported during CBD exposure may be attributed to the observation that 74% of the respondents reported the successful discontinuation of at least one antiseizure drug during CBD exposure. Of the 16 potential side effects addressed in this survey, only two were reported as more frequently encountered during CBD exposure: increased appetite ($p = 0.002$, McNemar) and weight gain ($p = 0.079$, McNemar). The effect on appetite does not seem to have been especially severe as 33 of the 35 respondents who reported an increase in appetite also reported continued CBD administration. After increased appetite and weight gain, the next most frequent side effect reported during CBD exposure was drowsiness (12.8%), and no other side effect was reported by more than 10% of the respondents during CBD exposure.

In addition to subjective efficacy and modest prevalence of side effects, many respondents reported improvement in sleep (53%), alertness (71%), and mood (63%). Notably, 93% of the respondents reported continued administration of CBD products at the time of survey completion.

4. Discussion

Although this study suggests a potential role for CBD in the treatment of IS and LGS in addition to SMEI, it does not represent compelling evidence of efficacy or safety. The limitations of the study design are of paramount importance. The use of an online-administered survey designed to ascertain subjective experiences with an open-label treatment readily introduces the possibility for numerous sources of confounding. Foremost, selection (participation) bias likely enriched the respondent cohort with patients who had favorable experiences during CBD exposure. The lack of placebo controls and unblinded self-assessment of efficacy and tolerability are clearly problematic. Although there were mechanisms in place to detect and prevent fraudulent responses, the veracity of responses could not be verified, and no website is completely secure. Indeed, the astounding response rate presented here may strike many readers as too good to be true.

These data would have been more compelling if the survey had been administered to a known cohort so as to validate responses and determine the rate of nonparticipation and, thus, estimate potential participation bias. In addition, had we demonstrated dose–response, this would have mitigated the concern that respondents may have been systematically biased. Conversely, the lack of dose–response does not necessarily increase suspicion of bias: the potential detection of a dose effect was underpowered as there were so few nonresponders and relatively few respondents who could report weight-based dosage. A lack of quality control and the inconsistency of CBD-enriched products obtained in the community may also have reduced rates of response or seizure freedom; CBD content (even when reported) could not be verified. In our clinical practice, we have observed several cases in which CBD content as determined by independent (and uncertified) laboratories operating in the community was considerably lower than advertised by manufacturers/distributors. Moreover, reported median CBD dosage was relatively low in our cohort.

There is likely to be considerable inaccuracy in our identification of patients' epilepsy syndromes. For the sake of feasibility, we did not employ validated diagnostic instruments. In our effort to assure confidentiality and avoid further participation bias (many parents have indicated that they are hesitant to report continued administration of an illegal drug given the potential legal ramifications), we did not request medical records, genetic diagnostic reports, or EEGs to verify syndromic classification. Such diagnostic confusion prevented us from reliably differentiating IS from LGS, as some patients with a parent-identified diagnosis of IS have either transitioned to LGS or met criteria for LGS and continue to suffer epileptic spasms. We suspect that some of the patients identified as IS and/or LGS in this study would not meet

formal clinical and electroencephalographic criteria for these disorders. Furthermore, we believe that the patients identified as IS represent a subpopulation with IS refractory to treatment as they did not receive CBD-enriched products early in the course of their epilepsy.

At face value, this study indicates that CBD-containing products might be effective and well tolerated in the treatment of multiple forms of refractory childhood epilepsy. Potential efficacy in the setting of IS and LGS is particularly exciting, but enthusiasm must be tempered by the absence of controlled data supporting this view. Rigorous clinical trials are clearly warranted and supported by these findings to determine the efficacy and safety of CBD. More broadly, the potential efficacy of CBD should be evaluated in children with less refractory epilepsy syndromes as well as in adults, especially as there are no data indicating age or syndrome specificity. Given the ease with which CBD products are obtained in many parts of the world—as well as the medical and even legal risks that presently accompany their use—practitioners, patients, and parents must proceed with caution and make efforts to distinguish between hope and empirical evidence.

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Disclosures/potential conflict of interests

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Dr. Sankar serves on scientific advisory boards for and has received honoraria and funding for travel from Acorda Therapeutics, Cyberonics, UCB Pharma, Sunovion, Upsher-Smith, and Lundbeck Pharma; receives royalties from the publication of *Pediatric Neurology*, 3rd ed. (Demos Publishing, 2008) and *Epilepsy: Mechanisms, Models, and Translational Perspectives* (CRC Press, 2011); serves on speakers' bureaus for and has received speaker honoraria from UCB, Supernus, Cyberonics, and Lundbeck. He has also received research support from the Bluebird Bio, Upsher-Smith, NIMH, and NINDS.

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