FULL-LENGTH ORIGINAL RESEARCH

Duration of use of oral cannabis extract in a cohort of pediatric epilepsy patients

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Summary

Objective: **Oral cannabis extracts (OCEs) are being used in the treatment of epilepsy with increasing rates in the United States following product legalization; however, no studies demonstrate clear efficacy. We evaluated the duration of use of OCEs as a measure of perceived benefit in a cohort of patients with pediatric epilepsy.**

Methods: **Retrospective chart review was performed of children and adolescents who were given OCEs for treatment of epilepsy.**

Results: **Of the 119 patients included in the analysis, 71% terminated use of their OCE product during the study period. The average length of use of OCE was 11.7 months (range 0.3–57 months). Perceived seizure benefit was the only factor associated with longer duration of treatment with OCE ($p < 0.01$). Relocation to Colorado was associated with perceived benefit of OCEs for seizures (65% vs. 38%, $p = 0.01$), but was not independently associated with longer OCE use. Factors associated with shorter use included adverse effects ($p = 0.03$) and a diagnosis of Dravet syndrome ($p = 0.02$). Twenty-four percent of patients were considered OCE responders, which was defined by a parent's report of a > 50% reduction in seizures while on this therapy. Adverse events (AEs) were reported in 19% of patients, with the most common side effects being somnolence and worsening of seizures.**

Significance: **Parental report of OCE use in refractory pediatric epilepsy suggests that some families perceive benefit from this therapy; however, discontinuation of these products is common. Duration appears to be affected by logical factors, such as perceived benefit and side effect profile. Surprisingly, families of patients with Dravet syndrome terminated use of OCEs more quickly than patients with other epilepsy syndromes. Results from this study highlight the need for rigorous clinical studies to characterize the efficacy and safety of OCEs, which can inform discussions with patients and families.**

KEY WORDS: **Epilepsy, Antiepileptic drugs, Pediatric, Cohort studies, Cannabidiol, Medical marijuana.**

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Among children with epilepsy, there exists a subset of patients whose families are choosing to pursue alternative therapies, either in place of or in combination with allopathic medications. Many of these patients have refractory epilepsy, and have failed to gain control of their seizures after trials of many medications and interventions.[1,2] There has recently been more attention paid to medical marijuana, in particular to strains that are high in cannabidiol (CBD) and low in tetrahydrocannabinol (THC), for the treatment of epilepsy.

Animal studies have suggested that marijuana has potential anticonvulsant properties. CBD is a known potentiator and inhibitor of some antiepileptic drugs (AEDs)[3,4]; however, independent action on endogenous receptors and ion homeostasis has also been demonstrated.[5] THC and tetrahydrocannabivarin (THCV) have also been shown to act on a

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Key Points

- Discontinuation of oral cannabis extracts is common in pediatric epilepsy patients
- Continuation of use of OCEs is predicted by perception of benefit on seizure burden
- Relocation to Colorado is significantly associated with a perception of seizure benefit of OCEs
- Termination of OCE use is predicted by a perception of adverse events related to the product
- A Dravet syndrome diagnosis predicts discontinuation of OCE use, which could be related to high baseline seizure frequency and lack of perceived seizure benefit

different set of receptors, also yielding antiseizure effects.[6,7] Many acute seizure models in mice suggest that treatment with CBD reduces the frequency and intensity of seizures[8,9]; however, few models of chronic epilepsy are in existence, and translation to the clinical setting has been imperfect.

Although clinical research is underway, there is currently a lack of well-designed, longitudinal, double-blind studies to support the use of oral cannabis extracts (OCEs) in refractory pediatric epilepsy.[10] A recently published open-label study suggested that CBD might be effective in reducing seizure frequency in children with treatment-refractory epilepsy,[11] and parental reports of patients with Doose, Dravet, and Lennox-Gastaut indicate that CBD helped to decrease seizure frequency.[1,2] However, in a separate review of four controlled studies examining the role of CBD in seizure treatment, no benefit of CBD was identified.[12] Particularly in pediatrics, the evidence that chronic marijuana exposure may be associated with cognitive dysfunction[13,14] is worrisome. In addition, a high rate of more-immediate side effects has been reported.[11]

The decision making process for families regarding use of OCEs for the treatment of pediatric epilepsy is not well understood. Particularly in children with severe epilepsy, families may turn to nonstandard treatments out of frustration with conventional medications and therapies.[15] Many families of patients with refractory epilepsy have chosen to relocate to Colorado to pursue OCEs since the legalization of marijuana for medical purposes in 2000 and widespread media coverage of anecdotal responses in 2011. In 2012, access to these products became easier, as retail sale of marijuana was also legalized in Colorado, although legislation required that patients establish residency in Colorado prior to initiating this treatment. As of April 2016, the Colorado Medical Marijuana Registry Program included 217 patients ages 0–10 years and 133 patients ages 11–17 years, with seizures being the most frequently cited indication for use.[16]

This research proposed to describe the duration of OCE use as a reflection of perceived efficacy of the product, as well as to characterize the factors affecting duration of use of OCEs among pediatric epilepsy patients at a tertiary care center. We hypothesized that discontinuation rates of OCE products would be affected by parents' perception of the benefits and side effects of the products, as well as by psychosocial factors such as socioeconomic status and whether the family moved to Colorado to access OCEs.

Methods

Retrospective chart review was performed for all children and adolescent patients whose parents had indicated that they were administering OCEs for treatment of epilepsy between December 2013 and July 2015. Patients were included in this study if they carried a diagnosis of epilepsy and had a documented seizure frequency both before and after initiation of OCEs. Subjects included were from 30 days to 18 years of age. Exclusion criteria were nondaily use of OCEs or if OCEs were used for reasons other than seizure control. Patients were considered to have moved to Colorado for OCEs if evidence of this relocation was documented in the electronic record.

All available clinical documentation was reviewed to obtain demographic data, seizure characteristics, seizure frequency, epilepsy syndrome, adverse events, type of OCE used and dosing (when known), number of concurrent AEDs, and reports of adverse events and nonseizure benefits. Epilepsy syndrome and seizure types were recorded as documented by the treating clinician, according to the International League Against Epilepsy (ILAE) classification. Seizure response was based on parental report of seizure frequency prior to initiating OCEs compared to the last documentation of seizure frequency while on OCEs. Patients were considered responders to OCEs if parents reported a > 50% reduction in seizure frequency. Additional nonseizure benefits and adverse events were based on patient, caregiver, and physician reports as documented in the medical record.

Study data were managed using the REDCap electronic data capture tool. Multiple Cox proportional hazard regression models were used to compare time to cessation of product between various patient factors. Tests of association between syndrome and seizure types and response to OCEs were done using Fisher's exact tests. Backwards selection was employed in order to choose the final Cox PH model; all variables that were significant at the $p = 0.05$ level were retained. This study was approved by the local institutional review board prior to any data analysis or collection.

Results

Demographic characteristics of the cohort are described in Table 1. Of the 119 patients included, 41% had relocated

with their families to Colorado prior to starting OCEs. Fifty-eight percent of all patients were privately insured at the time of data collection (Table 1). OCE product type (i.e. CBD vs. THC and/or brand name product) and dosing information were collected; however, this information was infrequently documented and thus was not analyzed. Seizure type and syndrome diagnoses (Dravet, Doose, and Lennox-Gastaut) are profiled in Table 2, along with the frequency of parentally reported response to OCEs.

Table 1. Demographic characteristics of the cohort

	Mean	Range
Age at initiation of OCE (years)	7.5	0.6–18
Duration of OCE tx (months)	11.7	0.3–57
	N	%
Moved to Colorado	46	41
Privately insured	65	58

tx, treatment.

Table 2. Prevalence of syndrome and seizure type in study cohort

Syndrome type	N	Responders (%)
Dravet	17	1 (6)
Doose	8	2 (25)
Lennox-Gastaut	19	11 (58)*
GTC	60	12 (20)
Absence	37	10 (27)
Myoclonic	31	8 (26)
Epileptic spasm	19	5 (26)
Tonic	30	12 (40)
Atonic	24	8 (33)
Focal	42	8 (19)

GTC, generalized tonic–clonic.
*$p < 0.05$ Fisher's exact.

Parents of 58 patients (49%) reported at least some improvement in seizures. Twenty-four percent of the cohort were considered to be responders to OCE treatment, which was defined as a > 50% reduction in seizure burden. Lennox-Gastaut syndrome (LGS) was the only syndrome type associated with a significantly higher proportion of responders when compared to all other patients in the cohort: 11 (58%) of 19 patients ($p < 0.05$). In a multiple Cox proportional hazard (PH) model, perception of any seizure benefit was the only factor significantly associated with longer duration of OCE use ($p < 0.01$, Fig. 1A). Syndrome type and seizure type were also included in the model; only Dravet syndrome emerged as significantly impacting duration of OCE use, and the presence of this diagnosis was associated with a shorter duration ($p = 0.02$, Fig. 1C). Relocation to Colorado was associated with perceived benefit of OCEs (65% vs. 38%, $p = 0.01$), but was not independently associated with longer use of OCEs. An interaction between relocation to Colorado and perception of seizure benefit was not significant, so it was excluded from the multiple Cox PH model. Nonseizure benefits of OCEs were also reported, including improved behavior/alertness in 46 patients (39%), improved motor skills in 9 (8%), and better sleep in 8 (7%).

Adverse events (AEs) due to OCE treatment were reported by parents of 23 patients (19%). The presence of adverse events was significantly associated with faster discontinuation of OCE treatment in the same multiple Cox PH model ($p = 0.03$, Fig. 1B). The most common AEs included worsening of seizures in 10 patients (8%), somnolence in 7 (6%), and gastrointestinal symptoms in 6 (5%). Eighty-four patients (71%) discontinued their OCE use during the study period. Of these 84 patients, only 13 (15%) had an adverse event and 8 (10%) carried a diagnosis of Dravet syndrome. Inversely, of the 23 patients that had an adverse event, 13 (57%) discontinued use.

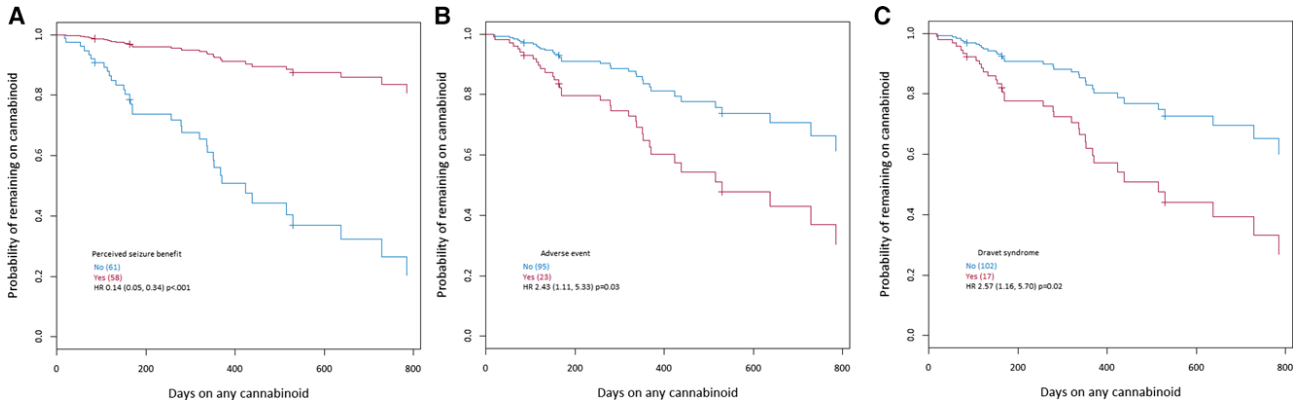

Figure 1.
Factors found to significantly impact duration of OCE use. Figures represent adjusted Kaplan-Meier curves for duration of OCE treatment based on (**A**) perceived seizure benefit, (**B**) reported adverse event, and (**C**) diagnosis of Dravet syndrome.

Discussion

Duration of use of OCEs in pediatric epilepsy patients follows some predictable patterns based on perception of benefit and AEs. Parental perception of benefit of OCEs on seizure profile is a key driver of continued use of OCEs; relocation to Colorado for OCEs has been shown to predict parental perception of benefit,[17] suggesting that sociologic factors may also play a role in medical decision making about OCEs. Remarkably, at least one third of patients who did not experience any seizure benefit continued to use OCEs at last follow-up, which could reflect use of the product for a nonseizure benefit. Relocation and the OCE products themselves are expensive and thus require financial commitment from the families; private insurance status was examined as a proxy for socioeconomic status, but did not emerge as a factor that significantly affected duration of OCE use.

Perception of AEs also affected duration of OCE use in a logical manner, as families reporting adverse events discontinued OCE use more quickly. Of interest, patients who experienced adverse events made up a relatively small percentage of the total subset of patients who discontinued OCE use. Although the presence of AEs was associated with an overall shorter time on product, some patients who report AEs continued to receive OCE treatments for an extended period, and >40% of the families reporting adverse events did not discontinue use of OCE (Fig. 1B). The adverse event rate in our cohort was notably lower than that of the large, open-label CBD trial that was recently reported[11] (19% vs. 79%), which may be related to the high dosing parameters in that trial. Most prescription AEDs also have AEs that have been found to impact quality of life,[18,19] and retention rates have been shown to be equal among first- and second-generation AEDs,[20] despite different side effect profiles. Many parents express specific concern about cognitive side effects of AEDs,[19] which was also seen in our cohort. Chronic exposure to marijuana is associated with poorer cognitive outcomes[21]; however, there are few data available on the impact of chronic exposure to specific marijuana derivative products on development, especially in patients who already have delays.

Response to OCE was variable. Patients with Lennox-Gastaut syndrome were the only group found to have a statistically significant rate of response to OCEs, with very low rates of response reported among Dravet and Doose syndrome patients. Among the cohort as a whole, the low response rate (24%) to OCEs was similar to the rate of placebo response seen in recent studies of four of the newer anticonvulsant medications (clobazam, perampanel, eslicarbazepine, and ezogabine) with rates of 31.6, 26.4, 20, and 21%, respectively.[22–25] This finding highlights the need for rigorous placebo-controlled studies of OCEs, especially within specific syndrome types, as there may be certain subgroups that benefit more than others.

Surprisingly, Dravet syndrome was associated with faster discontinuation of OCEs. This result was unexpected based on the media's portrayal of Dravet syndrome patients as having a positive response to OCEs. Because of this association, parents whose children carry a diagnosis of Dravet syndrome may have elevated expectations of efficacy and abandon this therapy more quickly if a positive effect is not apparent. In addition, these patients have a high seizure frequency, which may allow parents to judge whether the OCE is having an effect on seizure profile in a more expedited fashion as compared to patients with less frequent seizures. Of the 46 families of patients that moved to Colorado, 41% had a diagnosis of Dravet, Doose, or Lennox-Gastaut syndrome; of the cohort that did not relocate to Colorado, a similar percentage of patients carried one of these diagnoses (34%, $p = 0.6$).

Recall bias and the retrospective methodology are limitations of this study. The data relies heavily on parental report and provider documentation of the time frame, products, and perceived effects of OCEs, as well as on family decisions to alter prescribed AEDs with or without notifying their physician team. Chart review was performed in a retrospective fashion, and available information was limited by both parental disclosure to the treating provider as well as consistency in documentation between providers. The type and dosing of OCEs was not controlled with different OCE products utilized in individual patients. These products varied widely in their OCE concentrations, and some families used combination therapies with CBD and THC products. No serum levels of CBD or THC were obtained in these patients.

Our retrospective study of OCE use in pediatric epilepsy patients demonstrates that discontinuation of OCE products is common, and that patients whose families perceive the product to be beneficial for treating seizures continue the treatment for longer periods. Patients discontinue OCE treatment due to adverse events, but may also discontinue treatment due to more complex psychosocial issues related to their expectations of the efficacy of the product. The factors affecting parents' medical decision making process on behalf of children with chronic illnesses such as epilepsy are not well characterized. To better understand the efficacy and safety of cannabinoid therapies, we strongly support the need for controlled, blinded studies of products with consistent formulations in pediatric epilepsies that rely on concrete data such as daily seizure counts, formal neurocognitive assessments, and electroencephalography (EEG) as a possible biomarker.

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Disclosure

None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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