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Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy

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ABSTRACT

Objective: Oral cannabis extracts (OCEs) have been used in the treatment of epilepsy; however, no studies demonstrate clear efficacy. We report on a cohort of pediatric patients with epilepsy who were given OCE and followed in a single tertiary epilepsy center.
Methods: A retrospective chart review of children and adolescents who were given OCE for treatment of their epilepsy was performed.
Results: Seventy-five patients were identified of which 57% reported any improvement in seizure control and 33% reported a >50% reduction in seizures (responders). If the family had moved to CO for OCE treatment, the responder rate was 47% vs. 22% for children who already were in CO. The responder rate varied based on epilepsy syndrome: Dravet 23%, Doose 0%, and Lennox–Gastaut syndrome (LGS) 88.9%. The background EEG of the 8 responders where EEG data were available was not improved. Additional benefits reported included: improved behavior/alertness (33%), improved language (10%), and improved motor skills (10%). Adverse events (AEs) occurred in 44% of patients including increased seizures (13%) and somnolence/fatigue (12%). Rare adverse events included developmental regression, abnormal movements, status epilepticus requiring intubation, and death.
Significance: Our retrospective study of OCE use in pediatric patients with epilepsy demonstrates that some families reported patient improvement with treatment; however, we also found a variety of challenges and possible confounding factors in studying OCE retrospectively in an open-labeled fashion. We strongly support the need for controlled, blinded studies to evaluate the efficacy and safety of OCE for treatment of pediatric epilepsies using accurate seizure counts, formal neurocognitive assessments, as well as EEG as a biomarker. This study provides Class III evidence that OCE is well tolerated by children and adolescents with epilepsy.

1. Introduction

Epilepsy affects over 65 million people worldwide and approximately 2.3 million in the United States [1]. Approximately 1/3 of those have medically refractory epilepsy. Despite decades of research and the continued discovery of new antiseizure medications, seizures in many patients remain unresponsive to medical therapy. Many families choose to try nonpharmaceutical or alternative therapy options. Recently, there has been a surge of interest in the use of marijuana or *Cannabis sativa* and its extracted components. This interest has been fueled in part by recent media coverage of a specific strain of *Cannabis* reported to be high in cannabidiol (CBD) that is thought to be less psychoactive than strains containing higher levels of Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive component of cannabis.

A recent review analyzed four controlled studies which evaluated the role of CBD in seizure treatment, all of which had significant methodological flaws, and no benefit of CBD could be identified [2]. In a recent survey of parents of 19 children who were given CBD, more than 50% reported a dramatic decrease in seizures with no severe side effects [3]. There is also evidence that chronic marijuana use leads to a decline in cognitive function that may not be reversible [4,5].

Following favorable media coverage, OCE use has increased significantly in Colorado (CO). As part of the legislation, patients must have established residency in CO prior to initiating OCE treatment, leading to many patients moving from other states to establish care. The experience of a cohort of pediatric patients with epilepsy who were given OCE is reported.

2. Materials and methods

2.1. Subjects

We performed a retrospective chart review of children known to the neurology service at the Children's Hospital of Colorado who have trialed any OCE through July 2014. Children were included if they had epilepsy defined by the healthcare provider and a documented seizure frequency prior to starting OCE treatment. Additional inclusion criteria

Abbreviations: OCEs, Oral cannabis extracts; LGS, Lennox–Gastaut syndrome; AEs, Adverse Events; CO, Colorado; Δ^9-THC, Δ^9-Tetrahydrocannabinol.

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were a documented seizure frequency after initiating OCE treatment and documentation of at least two points of contact with a provider. Ages included were from 30 days to 18 years inclusive. Patients were excluded if they were not using OCE as a daily medication. Patients were analyzed with an intent to treat analysis. Patients were considered lost to follow-up if they were last reported to be on OCE and there was no patient contact for 6 months. This was based on the assumption that the patient likely returned to their home state as follow-up contact would be required for further medications refills.

2.2. Patient data

Data were extracted from the electronic medical record by the investigators and entered into a REDCap database. Outpatient, inpatient, telephone, and email encounters were reviewed including demographic data, seizure characteristics, seizure frequency, adverse events, type of OCE used and dosing, reports of additional benefits, and neurophysiology reports. Patients were considered to have moved to CO for OCE treatment if this was documented in the electronic record. Our practice was to not change medications while patients were on OCE, particularly during the titration phase. However, families sometimes reduced or discontinued medications without consulting with a neurologist.

2.3. Epilepsy classification and seizure control

Epilepsy and seizure types were classified according to the healthcare provider, reviewed by the investigators, and are reported based on the International League Against Epilepsy (ILAE) classification. Seizure response was based on parental report of total seizure frequency prior to initiating OCE treatment and at the last documentation of seizure frequency while on OCE. Responders were defined as a parental report of a >50% reduction in seizure frequency and consistent with the documented reported seizure frequencies. Additional benefits and adverse events were based on patient, caregiver, and physician reports.

2.4. Review of electroencephalography (EEG)

Available EEG reports were reviewed for changes in background. Since there was variation in the duration of the EEGs (routine versus prolonged), seizure frequency was not felt to be a reliable and consistent variable to ascertain. Improvement in the background EEG was based on a review of these reports by the investigators. Characteristics reviewed included well-formed posterior-dominant rhythms, frequency of interictal epileptiform discharges, spike–wave index, and overall organization during wakefulness and sleep.

2.5. Data collection and analysis

Study data were collected and managed using the REDCap electronic data capture tool. We analyzed the demographics including age at OCE initiation, gender, prior established care, type of OCE used, seizure type, and epilepsy syndrome. Factors affecting response to OCE were analyzed with χ^2 or Fisher's exact test and binary logistic regression. Seizure type responses were compared using ANOVA. Excel (Microsoft Inc., Redmond, Washington, USA) and SPSS Version 22 (SPSS Inc., Chicago, IL, USA) were used to perform the statistical analyses.

2.6. Standard protocol approvals, registrations, and patient consents

This study was approved by the local institutional review board prior to any data analysis or collection.

3. Results

Seventy-five patients were identified and met inclusion criteria. Thirty-four were male (45.3%), and thirty-four had moved to CO to obtain OCE (45.3%). The average age was 7.33 years (6 months to 18.25 years) when starting OCE treatment (Table 1). There were a variety of epilepsy syndromes in our cohort including Dravet, Doose and Lennox–Gastaut, as well as a variety of seizure types (Table 2).

Of the 75 patients, the parents of 43 (57%) reported at least some improvement in seizures. Twenty-five (33%) were reported to have a >50% reduction in seizures and were considered treatment responders. Two patients (0.3%) were reported to have seizure freedom at their last follow-up. One of these children had a history of febrile seizures; the other was initially having only 2–4 focal seizures a year. These were excluded from further analysis due to limited seizures at baseline. Two patients had epilepsy prior to starting OCE treatment, but were not actively having seizures at the time the treatment was initiated. One patient had an STXBP1 mutation and had worsening of seizures on CBD, and one had ESES with no improvement. If the family had moved to CO for OCE treatment, the responder rate increased to 16/34 (47%) vs. 9/41 (22%) (OR 3.16–95% C.I. 1.16–8.59 $p < 0.025$) if the family had established care in CO. There was no difference in responder rate based on seizure type. The responder rate varied based on epilepsy syndrome: Dravet 3/13 (23%), Doose 0/3 (0%), LGS 8/9 (89%) ($p < 0.05$) (Table 2). This statistical significance did not change when controlling for residency. Within the LGS group, no more than 3 patients reported the same seizure types despite many having more than 1 type of seizure.

When comparing various reported strains of OCE (i.e., high cannabidiol, high tetrahydrocannabinol) there was no difference in response rate (Table 3). Dosing information was collected; however, it was infrequently documented; thus it was not analyzed.

The average observation period was 5.6 months (range: 1–24 months). During this time, 11 (15%) patients discontinued their OCE use. Of the patients who discontinued OCE use, 7 (63%) had an adverse event, and 10 (91%) did not respond. However, responding to OCE or adverse events did not predict discontinuation in the overall sample. Only 10/50 (20%) of patients who did not respond to OCE discontinued treatment, and 7/33 (22%) of patients with an adverse event discontinued treatment with OCE. Five patients where lost to follow-up while still on OCE; one of whom was considered a responder at last follow-up.

Of the 30 patients with an electroencephalogram (EEG) prior to and during OCE treatment, only 3/30 (10%) had an improvement in their interictal EEG background. These changes included a decrease in spike–wave discharges, or improvement in background slowing. None of the 8 responders with EEG data had any improvement in their interictal EEG.

Many of the families reported benefits outside of seizure frequency including improved behavior/alertness in 25 (33%) patients, improved language (i.e., now using three words) in 8 (11%), and improved motor skills in 8 (11%) (Table 4). Adverse events (AEs) occurred in 33 (44%) patients with increased seizures (transient or persistent) or new seizures in 10 (13%), somnolence/fatigue in 9 (12%), GI symptoms in 8 (11%); rare adverse events occurred, including developmental regression in 2 patients, new movement disorder in 2, transient hemiparesis in 1, cholecystitis in 1, opisthotonus in 1, status epilepticus requiring intubation in 1, and death in 1 (Table 5). The single patient

Table 1
Demographic data.

Demographic data (N = 75)	Mean	(Range)
Age at initiation	7.33	(0.5–18.25)
Duration observed in months	5.59	(1–24)
	N	(%)
Male gender	34	45.30%
Moved to Colorado	34	45.30%