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Open-label use of Highly* purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes

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ABSTRACT

Objective: We studied our collective open-label, compassionate use experience in using cannabidiol (CBD) to treat epilepsy in patients with CDKL5 deficiency disorder and Aicardi, Doose, and Dup15q syndromes.
Methods: We included patients aged 1–30 years with severe childhood-onset epilepsy who received CBD for ≥10 weeks as part of multiple investigator-initiated expanded access or state access programs for a compassionate prospective interventional study: CDKL5 deficiency disorder (n = 20), Aicardi syndrome (n = 19), Dup15q syndrome (n = 8), and Doose syndrome (n = 8). These patients were treated at 11 institutions from January 2014 to December 2016.
Results: The percent change in median convulsive seizure frequency for all patients taking CBD in the efficacy group decreased from baseline [n = 46] to week 12 (51.4% [n = 35], interquartile range (IQR): 9–85%) and week 48 (59.1% [n = 27], IQR: 14–86%). There was a significant difference between the percent changes in monthly convulsive seizure frequency during baseline and week 12, $\chi^2(2) = 22.9$, $p = 0.00001$, with no difference in seizure percent change between weeks 12 and 48. Of the 55 patients in the safety group, 15 (27%) withdrew from extended observation by week 144: 4 due to adverse effects, 9 due to lack of efficacy, 1 withdrew consent, and 1 was lost to follow-up.
Significance: This open-label drug trial provides class III evidence for the long-term safety and efficacy of CBD administration in patients with treatment-resistant epilepsy (TRE) associated with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Adjuvant therapy with CBD showed similar safety and efficacy for these four syndromes as reported in a diverse population of TRE etiologies. This study extended analysis of the prior report from 12 weeks to 48 weeks of efficacy data and suggested that placebo-controlled randomized trials should be conducted to formally assess the safety and efficacy of CBD in these epileptic encephalopathies.
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1. Introduction

Severe epilepsies of childhood are associated with devastating neurodevelopmental delays. When cognitive, behavioral, and sensorimotor impairments exceed what is predicted from the underlying pathology, it is postulated that epileptic activity may directly impair function, i.e., epileptic encephalopathy (EE) [1]. Most EEs are associated with treatment resistant epilepsy (TRE), high medication burden, disabling comorbidities including cognitive slowing and/or regression, and increased mortality due to sudden unexpected death in epilepsy (SUDEP), status epilepticus, and drowning [2].

Common causes of EE include genetic epilepsies such as CDKL5 deficiency disorder and Dravet (DS), Dup15q, Aicardi, and Doose syndromes [1–6]. Seizures in these disorders are often resistant to available medication, dietary, or neurostimulation therapies. In many cases, existing therapies can cause or exacerbate cognitive, psychiatric, and motor disorders in addition to adverse systemic effects. There is a desperate need for safer and more effective antiseizure therapies for the EEs.

While recent randomized, placebo-controlled trials (RPCT) have demonstrated that an adjunctive oral, pharmaceutical formulation of Highly* purified CBD is a tolerable and effective treatment of two severe childhood-onset epilepsies, DS and Lennox–Gastaut syndrome (LGS) [5,6], prior open-label studies [7], anecdotal reports [8,9], and data from animal models [10,11] suggest that CBD may have antiseizure effects in a broad range of epilepsy syndromes and etiologies. Open-label studies found that CBD is effective in treating seizures associated with tuberous sclerosis and in febrile infection-related epilepsy syndrome (FIRES) [12,13]. However, a recent phase II RPCT of CBD for refractory focal epilepsy in adults using transdermal synthetic CBD failed to show a significant reduction in seizures in either the high-dosage or low-dosage groups over 12 weeks [14]. Systemic exposures to CBD in this study have not yet been reported. These discordant findings suggest that the efficacy of CBD may vary by seizure type, epilepsy syndrome, age, or route of administration [15]. Data from the open-label experience [7,12,13] with the oral, pharmaceutical formulation of CBD accurately predicted efficacy results (although no placebo data were available) of the subsequent phase III RPCT [6,20].

Beyond RPCTs for LGS and DS, there are limited data on other epilepsy syndromes, including many of the severe genetic epilepsies. We reviewed our collective open-label experience in using CBD to treat epilepsy in patients with CDKL5 deficiency disorder and Doose, Dup15q, and Aicardi syndromes. These groups were selected because the number of subjects studied in the open-label study was sufficiently large to justify subgroup analysis. There are currently no FDA-approved medications specifically for epilepsy occurring in patients with any of these syndromes.

2. Methods

Children and young adults with severe childhood-onset epilepsy who received CBD as part of multiple investigator-initiated expanded access programs or state access programs for compassionate use were enrolled in a prospective interventional study [7]. We identified cases of CDKL5 deficiency disorder (n = 20, 36%), Aicardi syndrome (n = 19, 35%), Dup15q syndrome (n = 8, 15%), and Doose syndrome (n = 8, 15%) at NYU Langone Medical Center, Massachusetts General Hospital, Lurie Children's Hospital, Pediatric and Adolescent Neurodevelopmental Associates (Atlanta, GA), Texas Children's Hospital, University of Utah Medical Center/Primary Children's Hospital, Wake Forest School of Medicine, and Nationwide Children's Hospital from January 2014 to December 2016. Concordant data were included from sites at the University of Iowa Hospitals and Clinics and University of Alabama in this extension. Patients treated included a group participating in the previous open-label CBD EAP analysis exploring CBD's antiseizure effects [7] as well as additional patients who began treatment after the prior study's enrollment cutoff, with all efficacy analysis including last observation carried forward (LOCF) through 48 weeks of follow-up and safety analysis through 144 weeks of extended follow-up.

After parents or patients provided informed consent and/or assent, the patients entered a four-week baseline period when parents/caregivers kept prospective seizure diaries. They were asked to focus on countable, discrete seizures with a sustained (>3 s) motor component (henceforth referred to as "convulsive seizures"). These include tonic–clonic, tonic, clonic, atonic, and focal seizures with prominent motor features. Although myoclonic, absence and nonmotor focal seizures with impaired awareness were counted, they were not considered part of the primary outcome measure. Convulsive motor seizures can be more reliably counted by observers than more subjective, nonconvulsive (impaired awareness) or transient (myoclonic seizure/jerk), phenomena in a child with an EE. We were concerned about potential parental bias based on their desire for benefit as well as the media attention and parental desire to be on CBD so we believe convulsive seizures to be the most objective measure for treatment effect.

Patients received a plant-derived pharmaceutical formulation of Highly* purified CBD, trade name Epidiolex (GW Pharmaceuticals, UK), in either a 25 mg or 100 mg per mL sesame oil-based solution. Cannabidiol at 5 mg/kg/day administered in two divided dosages was added to the baseline antiseizure drug regimen and then titrated every two weeks or less, as appropriate, by 2–10 mg/kg/day increments until intolerance or a maximum dosage of 25 mg/kg/day. At some sites, IRB and FDA allowed an increase to a maximum dosage of 50 mg/kg/day. For the first three months of CBD therapy, efforts were made to keep concomitant antiseizure drug dosages constant. In some cases, however, sedation due to elevations in concomitant antiseizure drug levels following the addition of CBD led to decreases in those drugs as clinically indicated. All seizures were recorded on paper diaries and reviewed by the study team at each visit. Tolerability and adverse effects were assessed every 2 weeks. In addition, we recorded use of rescue medications, episodes of status epilepticus, and emergency room visits/hospitalizations. Rescue medication use and organ function analysis was not performed because of lack of robust and consistent data.

The primary efficacy outcome measure was median percent change from baseline in monthly seizure frequency at the 12th and 48th week of the observation period for convulsive seizures, calculated as follows:

$$\text{Percent change in seizure frequency} = \frac{[\text{median monthly seizures (12 weeks)} - \text{median monthly seizures (baseline)}]}{\text{median monthly seizures (baseline)}} \times 100\%.$$

Percent change in mean monthly frequency for all seizures recorded by parents and each subtype was also calculated (secondary measures). Comparison between groups for percent change at each time point and for percent change over time was done using a Friedman test for nonparametric repeated measures. Those who did not characteristically exhibit convulsive seizures were not included in primary outcome analysis as change in convulsive seizure was the primary efficacy measurement. Patients whose participation was discontinued before, or had not yet reached the analysis endpoint of 48 weeks, or patients who did not report seizures for a scheduled interval were accounted for by a last-observation carried-forward analysis. As another secondary analysis, we assessed responders at each time period, defined as subjects whose mean reduction in monthly convulsive seizure frequency was 50% or greater. Responder rate was calculated from individual patient percent reductions. Statistics were performed using SPSS (Cary, NC).

The study was approved by the IRB at each institution.

3. Results

We analyzed data from 55 patients enrolled in our collective open-label use study between the dates of January 2014 and December 2016, with 55 (100%) in the safety group and 50 (91%) in the efficacy

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