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Cannabidiol is beneficial in management of drug-resistant Dravet syndrome

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Keywords: Cannabidiol, Dravet syndrome, epilepsy, seizures

Clinical Context
Aiden Williams (pseudonym), a 12 year old boy presented to neurology clinic for follow up of Dravet syndrome. He was diagnosed at 5 months old following a febrile generalized tonic clonic (GTC) seizure. He was found to have loss-of-function SCN1A mutations associated with Dravet syndrome. At that time he was placed on valproate. Due to the continued presence of four or more convulsive seizures a month, the patient's regimen was later modified. Currently, his antiepileptic drug (AED) regimen consists of valproate, clobazam, stiripentol and a ketogenic diet. His mother is concerned about continued episodes of about seven GTC seizures a month despite avoidance of triggers. His mother read an online blog about the new FDA approval of cannabidiol (CBD) as an adjunctive agent in treatment of drug-resistant seizures of Dravet syndrome. She would like to consider it as an option. She asked the team if CBD treatment could improve her son's seizure control. As a team, we felt it was appropriate to consider the addition of CBD.

Clinical Question
Is adjunctive cannabidiol a beneficial addition to current antiepileptic regimen in the treatment of children with drug resistant Dravet syndrome?

Research Article

Related Literature
The patient's mother found information about CBD on an online blog that focused on its current research and therapeutic applications. A PubMed search was conducted using the terms “Dravet Syndrome” and “cannabidiol” as well as “Cannabidiol Dravet.” References were also reviewed in articles on cannabidiol use in Dravet syndrome on UpToDate. This search resulted in sixty nine articles, with eleven specifically focusing on Dravet syndrome and cannabidiol therapy: three clinical trials with human subjects, one clinical trial with a mouse model, five commentaries, one review, and one case report. The review

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The Devinsky et. al 2017 paper was a placebo controlled, double blinded, randomized trial of 120 patients with drug resistant Dravet syndrome. The objective of the study was assessing the role of adjuvant CBD in reduction of convulsive seizure frequency. Patients who received CBD had greater reduction in convulsive seizure frequency when compared to patients who were given placebo, although the CBD group experienced higher rates of adverse events. The study methodology of this paper was superior to alternative papers due to the greater number of study participants combined with randomization, double blinding, and placebo group comparison. Additionally, a Nature review article on the use of CBD in treating Dravet syndrome found this therapeutic trial to be significantly informative in the field. For these reasons, I chose this paper for critical appraisal to evaluate whether adjunctive CBD therapy will improve seizure control of our patient.

Critical Appraisal
This double blinded, randomized, and placebo controlled multicenter study meets Category A and level 1 study quality with the SORT criteria. The primary outcome of the study was change in convulsive seizure frequency over a 14 week treatment period compared to a 4 week baseline. Secondary end-point measurements included: improvement or worsening in quality of life, reduction in total seizure and subtype seizure frequencies, sleep disruption, age-related behavior, number of hospitalizations due to epilepsy, number of patients with emergence of seizure types that did not present during the baseline period, and use of rescue medication. The team also looked at CBD safety profile by measuring number, type, and severity of adverse events. Thus the article considered both disease-oriented and patient-oriented outcomes.

This study recruited 120 participants aged 2-18 years old from 23 healthcare centers in the United States and Europe who were randomized into placebo (control) and cannabidiol (experimental) groups. Inclusion criteria included: an established diagnosis of Dravet syndrome, taking one or more AED’s, and having four or more convulsive seizures during the 28-day baseline period. Exclusion criteria was not defined. The patients in the study were on an average of three AED’s with continued seizure activity. Both the number and type of drugs used to manage Dravet syndrome in a setting of continued drug-resistant epilepsy match our patient’s profile.
All patients were first observed for a 4 week baseline period prior to initiation of 14 weeks of therapy followed by an option to enroll in an open label extension study or continue with 10 day taper and 4 week safety follow up period. Both groups continued to receive their standard AED regimen. In addition, the experimental group (N = 61) received a 20 mg/kg/d solution of CBD twice daily while the control group (N = 59) received a placebo solution infusion of the same quantity and frequency. Experimental and control groups were reasonably similar apart from unequal distribution of sex with 57% of the experimental group male versus 46% of the control group. At the end of treatment, nine withdrew from the experimental group, eight due to adverse events and one due to non-adherence, for a total of 52 completing the trial. Adverse events included: diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal liver function tests. In contrast, three withdrew from the control group due to adverse events and a total of 56 completed the treatment period. Therefore a total of 90% completed the full trial, 85% of the experimental group and 95% of the control group.

Analysis of both groups revealed a significant reduction in convulsive seizure frequency in the experimental group (38.9%) compared to control (13.3%) with p = 0.01 and NNT = 4. Thus, there was a large effect size difference supporting the use of CBD in treating convulsive seizures. However, there was no significant change in frequency of non-convulsive seizures between groups which may either be due to inability of caregivers to recognize the episodes or CBD’s mechanism of action. All other secondary outcomes were also insignificantly changed between groups. Of note, adverse events occurred significantly more in the experimental group and with greater severity (16% in experimental versus 5% in control). One limitation of the study was that the adverse events may have unblinded patients and caregivers to which treatment group they were randomly assigned to. A post hoc analysis by investigators addressed this pitfall and found no relationship between somnolence, the most common adverse event, and the treatment effect.

Another limitation of the study was funding by GW Pharmaceuticals, a company that focuses on cannabinoid drugs and which provided the CBD used by investigators. Employees of the funding agency were involved with study design, data analysis, and compilation of the article which increases risk of sponsorship bias.

Overall despite minor flaws, this study showed CBD caused a statistically significant reduction in convulsive seizure frequency for Dravet syndrome patients with drug-resistance. CBD can feasibly be added to current AED regimens with close monitoring for adverse events.

Clinical Application

Ultimately, there is ongoing research about the use of CBD in epilepsy management. In June 2018 based on this current body of research, the FDA approved cannabidiol oral solution for treatment of seizures associated with Dravet syndrome and Lennox-Gestaut syndrome. This opens up a new therapeutic option for physicians and patients thus necessitating a discussion of CBD use based on scientific evidence of benefits and risks.

Based on this study, CBD significantly decreased frequency of convulsive seizures. This conclusion was relevant to Aiden, who suffered from GTC seizures. It is important to ascertain from the patient or caregiver what seizure type the patient suffers from when considering adjunctive CBD. Additionally, during treatment close monitoring is required due to higher incidence and severity of adverse events. Furthermore, caregivers require education on administration of CBD along with the tapering process if treatment is discontinued. Aiden and his mother as his caregiver were able to decide in favor of adjunctive CBD therapy after discussion of the benefits versus risks of therapy. When asked what the patient sought with treatment, he identified control of his convulsive seizures as his primary goal and we as his care team felt the CBD could help achieve this goal. In the end, Aiden, his mother, and us, his care team, were all hopeful CBD would improve seizure control.

Learning points:
1. Cannabidiol benefits Dravet syndrome patients with drug-resistant convulsive seizures by reducing seizure frequency.
2. Cannabidiol comes with risk of adverse events, primarily somnolence, which may limit tolerability of treatment.

Management of children with epileptic syndromes requires coordination between their caregivers, who may derive medical information from online sources, and physicians.

References