Governing Iowa's public universities and special schools

University of Iowa
Iowa State University
University of Northern Iowa
Iowa School for the Deaf
Iowa Educational Services for the Blind and Visually Impaired
Lakeside Laboratory Regents Resource Center
Western Iowa Regents Resource Center

BOARD OF REGENTS
STATE OF IOWA

Michael J. Richards, MD, President, *West Des Moines*
Sherry Bates, President Pro Tem, *Scranton*
David R. Barker, PhD, *Iowa City*
Robert Cramer, *Grimes*
Abby Crow, *Tiffin*
Nancy Dunkel, *Dyersville*
Jim Lindenmayer, PhD, *Ottumwa*
JC Risewick, *Johnston*
Greta Rouse, *Emmetsburg*

Mark J. Braun, EdD, Executive Director

June 30, 2023

Mr. Charlie Smithson
Secretary of the Senate
State Capitol Building
Des Moines IA 50319

Ms. Meghan Nelson
Chief Clerk of the House
State Capitol Building
Des Moines IA 50319

Kelly Garcia, Director
Iowa Department of Health & Human Services
Hoover State Office Bldg
Des Moines, IA 50319

Re: 2023 Report on Use of Medical Cannabidiol

Dear Members of the Iowa General Assembly and Director Garcia:

Pursuant to the 2014 Iowa Acts Ch 1125, §10h, enclosed is the 2023 report on Report on Use of Medical Cannabidiol.

If you have any questions or need more information, please don't hesitate to contact this office.

Sincerely

Mark J. Braun

Re: **2023 Report to the Department of Public Health and the Iowa General Assembly regarding Cannabidiol and Epilepsy**

Recent Publications and additions since the last review submitted July 2022:

In a PubMed.gov search with the search criteria of “cannabidiol,” “epilepsy,” and “randomized control trial” only one study was returned. A search utilizing the criteria of “cannabidiol,” “epilepsy,” and “clinical trial,” five further studies were reported, although Li et al. was not a clinical study determining efficacy in epilepsy in humans.

Randomized controlled trial:

- The randomized control trial was a multicenter trial in Australia and New Zealand by O’Brien et al. that enrolled adults with drug resistant epilepsy and were on 0-3 antiseizure medications. The patients were randomized to placebo, 195mg, or 390mg transdermal patches of cannabidiol. The trial took 12 weeks. The patients were then offered enrollment in an open-label extension study in which all participants were placed on active drug. “**Results:** A total of 188 patients (45% male [85 patients] and 54.8% female [103 patients]) with a mean (SD) age of 39.2 (12.78) years were randomized, treated, and analyzed (195-mg cannabidiol, 63 participants; 390-mg cannabidiol, 62 participants; placebo, 63 participants). At week 12 of the double-blind period, there was no difference in seizure frequency between placebo (mean [SD] 2.49 [1.31] seizures per 28 days) and 195-mg cannabidiol (mean [SD] 2.51 [1.15] seizures per 28 days; least squares mean difference, 0.014; 95% CI, -0.175 to 0.203; P = .89) or 390-mg cannabidiol (mean [SD] 2.59 [1.12] seizures per 28 days; least squares mean difference, 0.096; 95% CI, -0.093 to 0.285; P = .32). By month 6 of the open-label extension, 115 patients (60.8%) achieved a seizure reduction of at least 50%. Treatment-emergent adverse events occurred in 50.4% (63 of 125 participants) of the cannabidiol group vs 41.3% (26 of 63 participants) in the placebo group, with a treatment difference of 9.1% (95% CI, -6.0% to 23.6%), and occurred at similar rates in the cannabidiol groups. Few participants discontinued (7% [14 of 188 participants]), and most (98% [171 of 174 participants]) continued into the open-label extension. **Conclusions and relevance:** Both doses of transdermal cannabidiol were well tolerated and safe. No significant difference in efficacy was observed between cannabidiol and placebo during the double-blind treatment period. The open-label extension demonstrated the long-term safety, tolerability, and acceptability of transdermal cannabidiol delivery.”

Clinical trials:

- Peters et al. noted: People with epilepsy may experience episodes of frequent seizure activity (seizure clusters, acute repetitive seizures), and benzodiazepines are the cornerstone of rescue treatment. Cannabidiol (CBD) can be used as an adjunctive treatment for epilepsy, and it may interact with other antiseizure drugs, such as benzodiazepines. Here, we examined the safety and effectiveness of intermittent use of diazepam nasal spray in patients with seizure clusters who also received CBD treatment. This analysis included data from patients aged 6 to 65 years enrolled in a phase 3, long-term safety study of diazepam nasal spray. Age- and weight-based dosing of diazepam nasal spray were administered during a 12-month treatment period. Concomitant CBD use was recorded, and treatment-emergent adverse events (TEAEs) were

collected. Of 163 treated patients, 119 (73.0%) did not receive CBD, 23 (14.1%) received the US Food and Drug Administration-approved highly purified CBD and 21 (12.9%) received another form of CBD. On average, patients receiving highly purified CBD were younger and more likely to have epileptic encephalopathies, including Dravet syndrome or Lennox-Gastaut syndrome, than patients who received another CBD preparation or no CBD. Rates of TEAEs and serious TEAEs were greater in patients who received any form of CBD (90.9% and 45.5%, respectively) compared with no CBD (79.0% and 26.1%, respectively). However, the lowest rates of TEAEs attributed to diazepam nasal spray were reported in patients who received highly purified CBD (13.0%), and this result was maintained in those who received concomitant clobazam. Use of second doses of diazepam nasal spray, a proxy for effectiveness, was lowest in the highly purified-CBD group (8.2%) compared with the no-CBD (11.6%) and other-CBD groups (20.3%). These results suggest that CBD does not alter the safety and effectiveness of diazepam nasal spray and supports concomitant use in appropriate patients.

- Georgieva et al. noted: **Objective:** Epidiolex® (CBD) is FDA-approved for seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), and tuberous sclerosis complex (TSC). Phase III studies suggest that certain adverse effects (AEs), possibly linked to pharmacokinetic/pharmacodynamic (PK/PD) interactions may be therapy-limiting. We sought to identify these factors that contribute to treatment success and retention of therapy. **Methods:** A single-center, retrospective review of patients with refractory epilepsy taking Epidiolex® was performed. Kaplan-Meier analysis was performed to describe Epidiolex® retention, as a measure of overall effectiveness. **Results:** One hundred and twelve patients were screened; 4 were excluded due to loss to follow-up or never starting Epidiolex®. Of 108 patients, mean age was 20.3 years (13.1, range 2 to 63), and 52.8% were female. Mean initial and maintenance doses were 5.3 mg/kg/day (1.3) and 15.3 mg/kg/day (5.8), respectively. At the final evaluation, 75% of patients remained on Epidiolex®. The 25th percentile for discontinuation was 19 months. 46.3% of patients experienced at least one treatment-emergent adverse effect (TEAE) with 14.5% d/c Epidiolex® due to treatment emerging adverse effects (TEAE). The most common reasons for discontinuation were lack of efficacy (37%), increased seizure activity (22%), worsened behavior (22%), and sedation (22%). One out of 27 discontinuations was due to liver function test (LFT) elevations (3.7%). At initiation, 47.2% were concurrently taking clobazam, and 39.2% of those patients had an initial clobazam dose decrease. 53% of patients were able to either discontinue or lower the dose of at least one other antiseizure medication. **Significance:** Epidiolex® is generally well-tolerated and the majority continued long-term treatment. Patterns of adverse effects were similar to clinical trials, however gastrointestinal complaints, and significant LFT elevations were less common. Our data suggest most patients discontinue within the first several months of treatment and suggest that further studies designed to evaluate early identification and potential mitigation of adverse effects and including drug interactions are warranted.

- Smegal eta l. noted: **Background:** A prior drug trial of cannabidiol for treatment-resistant epilepsy in patients with Sturge-Weber syndrome (SWS), a rare neurovascular condition, implicated improvements in neurological, quality of life (QOL), neuropsychologic, psychiatric, and motor outcomes.**Methods:** Ten subjects with SWS brain involvement, controlled seizures, and cognitive impairments received study drug in this Johns Hopkins institutional review board-approved, open-label, prospective drug trial. Oral cannabidiol was taken for six months (dose ranged from 5 to 20 mg/kg/day). SWS neuroscore, port-wine birthmark score, QOL, and adverse events were recorded every four to 12 weeks. Neuropsychologic, psychiatric, and motor assessments were administered at baseline and six months' follow-up. Most evaluations were conducted virtually due to the coronavirus disease 2019 pandemic.**Results:** Cannabidiol was generally well tolerated. Six subjects reported mild to moderate side effects related to study drug and continued

on drug; one subject withdrew early due to moderate side effects. No seizures were reported. Significant improvements in SWS neuroscore, patient-reported QOL, anxiety and emotional regulation, and report of bimanual ability use were noted. Migraine QOL scores were high at baseline in these subjects, and remained high. Neuropsychologic and other QOL and motor outcomes remained stable, with some within-subject improvements noted. **Conclusions:** Further studies are needed to determine whether Epidiolex can improve quality of life and be beneficial for neurological, anxiety, and motor impairments in SWS independent of seizure control. Large multicentered studies are needed to extend these preliminary findings.

- Navarro noted: **Introduction:** The safety and efficacy of a formulation high in cannabidiol (CBD) and low in Δ^9-tetrahydrocannabinol (THC) to treat drug-resistant epilepsy have been examined previously in children, but not in adult population. The aim of this study was to evaluate whether CBD-rich oil, as an add-on treatment to conventional antiepileptic drugs, was effective, safe, and well-tolerated in adults with drug-resistant focal epilepsy (DRFE). M**ethods:** An open-label, prospective cohort, single-center in adult patients with DRFE, were receiving stable doses of antiepileptic drugs (AEDs). A cannabis based-magistral formulation (CBMF) (100 mg/ml CBD and THC <1.9 mg/ml) was administrated 0.1 ml sublingually every 12 hours, up-titrated weekly. The primary outcome was to establish a reduction in seizures frequency >50% at 12 weeks. Adverse-drug reactions monitoring was done. p-value <0.05 was statistically significant. **Results:** Between August 2020 and July 2022, 44 (38.6%) patients completed >3 months of follow-up. The median daily dose of CBD was 200 mg, that of THC was 4 mg, and that of CBD per kilogram of weight was 3.7 mg. The median number of seizures per month before CBD treatment was 11, and after CBD treatment was 2.5 ($p<0.001$). A reduction in seizures >50% at 12 week was achieved in 79.5% of the patients. The median percentage change in seizure frequency per month was 84.1% at 12 weeks. Five patients reported any adverse-drug reactions. **Conclusion:** The CBMF is a highly effective and safety therapy to treat adult patients with DRFE. The reduction in seizures frequency is maintained over time.

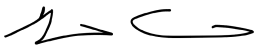
Bottom line from these studies:

- CBD via the transdermal route does not seem to be efficacious in drug resistant adults.
- CBD seems to be generally well tolerated and efficacious in tuberous sclerosis complex and Sturge-Weber syndrome.
- CBD does not result in diminished efficacy of diazepam for prolonged seizures
- An uncontrolled trial of a CBD/THC combined product was tolerated in adults and resulted in seizure reduction in some participants

References

1. O'Brien TJ, Berkovic SF, French JA, Messenheimer JA, Sebree TB, Bonn-Miller MO, Gutterman DL; STAR 1/STAR 2 Study Group. Adjunctive Transdermal Cannabidiol for Adults With Focal Epilepsy: A Randomized Clinical Trial. JAMA Netw Open. 2022 Jul 1;5(7):e2220189. doi: 10.1001/jamanetworkopen.2022.20189. Erratum in: JAMA Netw Open. 2022 Aug 1;5(8):e2228862. Erratum in: JAMA Netw Open. 2022 Dec 1;5(12):e2249107. PMID: 35802375; PMCID: PMC9270696.
2. Peters JM, Puri V, Segal E, Misra SN, Rabinowicz AL, Carrazana E. Concomitant cannabidiol does not impact safety and effectiveness of diazepam nasal spray for seizure clusters: Post hoc analysis of a phase 3 safety study. Epilepsy Behav. 2023 Jul;144:109248. doi: 10.1016/j.yebeh.2023.109248. Epub 2023 May 19. PMID: 37210793.
3. Georgieva D, Langley J, Hartkopf K, Hawk L, Margolis A, Struck A, Felton E, Hsu D, Gidal BE. Real-world, long-term evaluation of the tolerability and therapy retention of Epidiolex® (cannabidiol) in patients with refractory epilepsy. Epilepsy Behav. 2023 Apr;141:109159. doi: 10.1016/j.yebeh.2023.109159. Epub 2023 Mar 7. PMID: 36893722.
4. Li J, Zagorski JW, Kaminski NE. Establishment of a point of departure for CBD hepatotoxicity employing human HepaRG spheroids. Toxicology. 2023 Apr;488:153469. doi: 10.1016/j.tox.2023.153469. Epub 2023 Feb 28. PMID: 36863504.
5. Smegal LF, Vedmurthy P, Ryan M, Eagen M, Andrejow NW, Sweeney K, Reidy TG, Yeom S, Lin DD, Suskauer SJ, Kalb LG, Salpekar JA, Zabel TA, Comi AM. Cannabidiol Treatment for Neurological, Cognitive, and Psychiatric Symptoms in Sturge-Weber Syndrome. Pediatr Neurol. 2023 Feb;139:24-34. doi: 10.1016/j.pediatrneurol.2022.10.014. Epub 2022 Nov 12. PMID: 36508880.
6. Navarro CE. Cannabis-based magistral formulation is highly effective as an adjuvant treatment in drug-resistant focal epilepsy in adult patients: an open-label prospective cohort study. Neurol Sci. 2023 Jan;44(1):297-304. doi: 10.1007/s10072-022-06393-1. Epub 2022 Sep 21. PMID: 36129615.

Sincerely,



Michael Ciliberto, MD
Associate Professor
Division of Pediatric Neurology
Stead Family Department of Pediatrics
University of Iowa Children's Hospital