Cannabidiol as a Treatment for Behavioral Issues in Pediatric Patients With Intellectual Disabilities

A pediatric critical care physician provides commentary on a recent study: Efron D, et al. Does cannabidiol reduce severe behavioural problems in children with intellectual disability? Study protocol for a pilot single-site I/II randomized placebo-controlled trial. *BMJ Open.* 2020;10(3):e034362.

By Eric Exelbert, MD

Pediatric Critical Care Physician, Joe DiMaggio Children's Hospital, Hollywood, Florida
Director of Pediatrics, CED Clinic
Founder, ExAlt Med, LLC

Pediatric patients with intellectual disabilities (ID) and severe behavioral problems (SBP) represent one of the most challenging populations to treat and for which to provide a safe medical home. Parents or guardians of children with ID and SBP often find they have exhausted their financial means, community-based support, and medical options. The struggles faced by caregivers of children with ID/SBP also place a severe strain on family and loved ones, sometimes resulting in broken homes and worsening of the patient's condition.

As many US states have adopted medical and recreational cannabis programs, the use of medical cannabis for a number of qualifying conditions has been brought to the forefront of modern medicine. The pediatric population has become one of the most important and controversial populations to enter into this realm of therapy. Although the American Board of Psychiatry and Neurology and the American Academy of Pediatrics do not support the use of medical cannabis to treat mental health disorders, both organizations do recognize and underscore the need for more research in this area. As a practicing pediatric intensive care physician who also provides consultations for medical cannabis, I find pediatric patients with ID/SBD are one of the most difficult populations to treat. In addition to everyday minute-to-minute basic care, these patients also require specialized care and attention for medical procedures, sedation, simple checkups with a medical professional, or just attending school.

In this commentary, I address not only this specific population of patients, but also the endocannabinoid system (ECS) and use of cannabidiol (CBD) as a possible medical adjunct to conventional medical therapy in relation to the study by Efron et al.[1] In their paper, the authors describe a pilot single-site, phase I/II randomized placebo-controlled trial, the primary aim of which is to assess the feasibility of conducting a double-blinded, randomized controlled trial of CBD in pediatric patients with ID/SBP. The authors' secondary study aim is to collect preliminary data on the safety and tolerance of CBD in this patient population, which they hope will help to evaluate and determine the elements necessary to produce future quality evidence-based trials, as well as obtain data on the safety of administering CBD to this population.

Dr. Exelbert has no financial disclosures to report.

CBD for Children With Intellectual Disabilities

continued from page 43

TABLE. Ongoing Registered Trials Reporting Behavioral Outcomes of Youth Treated With Medicinal Cannabis Products

Sample size	Population	Study design	Product used	ClinicalTrials.gov Identifier
150	Youth with ASD+SBP	Double-blind, crossover RCT	Cannabis oil with a 20:1 ratio of CBD to delta-9-THC	NCT02956226
100	Children with ASD+SBP	Double-blind RCT	Cannabidivarin (CBDV; a homolog of CBD)	NCT03202303
26	Youth with Prader-Willi syndrome +SBP	Double-blind RCT	CBDV	NCT03848481
204	Children with Fragile X syndrome	Double-blind RCT	Synthetic CBD	NCT03614663

ASD, autism spectrum disorder; **CBD,** cannabidiol; **ID,** intellectual disability; **RCT,** randomized controlled trial; **SBP,** severe behavioral problem; **THC,** delta-9-tetrahydrocannabinol.

Reprinted from Efron et al.[1]

In this study, 10 patients ranging from 8 to 16 years of age will be randomized 1:1 to receive 98% CBD (from a single source [Tilray, Canada]) in grapeseed oil or placebo grapeseed oil (the placebo oil will be matched for smell, taste, and appearance). Patients in the CBD group will receive an initial daily dose of 5 mg/kg divided twice daily; this dose will be increased by 5 mg/kg every 3 days for 9 days to a maintenance dose of 20 mg/kg/d ("uptitration phase"). This maintenance dose will be maintained for 8 weeks ("maintenance phase"); thereafter, the dose will be decreased by 5 mg/kg for 9 days, after which time administration will cease.[1]

Small Sample Size of a Large Population With Varying Degrees of Impairment

The intent and purpose of this study is excellent: The authors seek to improve the quality of life for patients with ID/SBD, as well as to expand the number of therapy choices available to them. Although there is a large population from which the authors may recruit for this study, not all patients with ID/SBD have the same level of impairment. One of my first thoughts as I read through this pilot study concerns the variability in the degree of impairment that exists among patients with ID/SBD. Although the goal of the study is the feasibility of the trial in this patient population, feasibility in this case may not equate with a high statistical power. There are many different etiologies of ID/SBP, each with possible genetic/inherited, metabolic, traumatic, or idiopathic etiology. The intent of the investigators to recruit only 10 patients does not represent a good a sample size and may not truly provide answers to intended questions of the study. Although 10 patients is a feasible number, it may not be reliable for the answers sought to be answered by this study based on the number of conditions and variability in degree of impairment among patients with ID/SBD.

Down syndrome, Rett syndrome, and autism spectrum disorder (ASD; formerly referred to as pervasive developmental disorder) are examples of some of the conditions associated with ID/SBD. Down syndrome is the most common chromosomal disorder in the United States, affecting about 1 in every 700 babies born.[2] Fragile X syndrome is the most commonly known cause of inherited ID with females having milder symptoms. It is estimated that 1.4 per 10,000 males and 0.9 per 10,000 females have fragile X syndrome.[3] Rett syndrome is a neurodevelopmental disorder and occurs almost exclusively in females, and the specific mutation causing the syndrome is the gene *MECP2*.[4] It is estimated to have an incidence about 1 per 23,000 live female births.[5] Lastly, statistics show that 1 in 68 (1.6%) 8-year-old children receive a diagnosis of ASD, with a male-to-female ratio of 4:1.[6] ASD can be a primary diagnosis or can be part of another diagnosis such as those previously mentioned, as well as many other conditions.

Moreover, it is important to note that the level of developmental and behavioral impairment can range from mild to severe, not only among patients who share the same or similar disorders or syndromes, but also among those with ID/SBD of other etiologies. Therefore, the study needs to consider the various degrees of ID among patients. This is significant because not all patients with ID/SBD have an intelligence quotient <70,[3] which is listed as a prerequisite for this study.

ECS and Behavioral Processes in Patients With ID/SBD

Taking this one step further, the ECS modulates several physiologic processes and behavior responses in these diseases/syndromes, and ECS deregulation has been associated with many different neuropsychiatric disorders.[7] For instance, there are data suggesting pathology or dysregulation of the ECS in patients with ASD.[8] So how will one be able to ascertain the possible benefit or detriment of CBD in patients with potentially different types of ECS pathology? Also, how do we know that the patient's daily medication regimens are not disrupting the ECS? If we now add a phytocannabinoid, in this case CBD, to the patient's medical regimen, can we discern exactly what is being manipulated or palliated within the ECS that attempts to render it more efficient? How do we determine which, if any, of the individual pathways that make up the ECS of these patients are faulty and how such dysfunction should be addressed? I can tell you clinically in my practice that I have observed patients with some of the specific syndromes I mentioned earlier who did horribly when given a low dose of CBD but who did better when treated with high doses of CBD (these patients required quicker upward titration of CBD). CBD alone, however, usually was not sufficient. For example, in my practice, we would see an initial quick response in patients given CBD, with some mild improvements in mood, sleep, and behavior. However, these effects were short-lived, and most patients required increased doses of CBD or the addition of delta-9-tetrahydrocannabinol, cannabidiolic acid, or cannabigerol, where available. Additionally, generating this type of clinical information took longer than the 8 weeks proposed in the authors' pilot study to see the potential clinical manifestations. Feasible or reliable?

Dosing Schedule, Uptitration Interval, and Length of Therapy

Understanding that a secondary aim of this study is to determine the safety and tolerance of CBD in these patients, the second concern I have relates to the dosing schedule for the CBD (in the form of mg), the interval for the uptitration of the CBD, and again the length of therapy. The dosing of CBD for the authors' pilot study was based on a trial by Devinsky et al.[9] in patients with Dravet syndrome, a severe form of epilepsy wherein patients can experience hundreds of seizures daily. In this trial, Devinsky et al.[9] concluded that "cannabidiol resulted in a greater reduction in convulsive-seizure frequency than placebo and was associated with higher rates of adverse events." Based on these findings, the authors felt the pharmacokinetic (PK) profile is a good match for their study population.

In the Dravet study, the main side effects were considered mild; these included somnolence, diarrhea, and decreased appetite (36%, 31%, and 28%, respectively). Some effects were severe, such as elevation of liver transaminases (~16.3%). Althoug h these adverse effects are relatively mild, I am not sure the doses of CBD given to patients in the Dravet trial are appropriate for this pilot study population. One can make the argument that the high dosages used in the Dravet study are directly associated with the adverse effects experienced by some participants. How can we compare a dosing strategy for one disease when we do not know the correct dosing for the ID/SBP patient? Also, will the side effects make the feasibility of the study difficult? The pilot study is looking at a completely different population—one that does not experience such frequent or life-threatening seizures (although some patients can).

> The pediatric population has become one of the most important and controversial populations to enter into this realm of therapy.
>
> —ERIC EXELBERT, MD

The authors, however, are looking at a population that has heightened sensorium, behavioral outbursts that can be physically challenging to manage, and who are on medications that are metabolized by the liver (eg, most antipsychotic drugs), the combination of which can be detrimental. A patient with ASD with heightened sensorium may "act out" when he or she has horrific diarrhea. Similarly, the ID/SBP patient who experiences sleepiness as a side effect of CBD may combat this feeling with worsened behavior. One might conclude that this is a typical side effect of the CBD and it affects the child's minute-to-minute behavior, but is it related to the dose, the oil, the patient's absorption of CBD, or the interactions with the other medications the patient is taking? Would we call this a treatment or safety failure if the side effect outweighs the benefit? Again, in my clinical experience, patients with ID/SBD require a much broader range of CBD, and it was always hard to tease failures and successes with just one cannabinoid.

In my experience, both patients with ID/SBD and their families are already in turmoil, and their patience is slim. Additionally, parents of patients with ID/SBD are very involved in their care and medical regimen and know their children very well, both from a pharmacologic perspective and, of course, their parental perspective. For

CBD for Children With Intellectual Disabilities

continued from page 45

example, within 1 to 2 days of starting or changing a patient's cannabinoid, parents often email or call me with concerns and questions, sometimes blaming a change in their child's behavior on the CBD or another cannabinoid. It takes patience, good listening, and a deep understanding of these patients, as well as the goals of their parents that led them to seek medical cannabis for their child.

> I recommend consistency with respect to timing of the cannabinoid administration and the patient's diet.
>
> —ERIC EXELBERT, MD

Factors That May Affect the Pharmacokinetics of CBD

The final concern I have with this article, again knowing that feasibility is the primary end point, is related to a much broader question, one that physicians have yet to figure out: CBD administration and PKs. How do the administration times, daily diet, route of administration (eg, orally vs through a gastrostomy tube; this study only mentions oral administration), and hydration status affect a patient's response to CBD? Does it matter if a patient takes the CBD with a fatty or non-fatty meal, with other prescribed medications, at the same time each day, or if they have an altered hydration status? These are the types of questions that I discuss all the time with families at my clinic, and I do not have all the answers. I do recommend consistency with respect to timing of the cannabinoid administration and the patient's diet, with the goal of limiting the uncontrolled variables and honoring those that are controlled. We do know that endocannabinoids are made from membrane lipids using enzymes that are responsible for their synthesis, transport, and degradation.[10] Recent data suggest that the bioavailability of CBD after oral dosing with fasting is 6% and can increase 4-fold when it is coadministered with a fatty meal.[11] Furthermore, because CBD is metabolized almost exclusively in the liver, 70% to 75% of oral CBD will be removed in the liver before reaching the systemic circulation; then a patient's diet may further decrease the gastrointestinal absorption of CBD.[11]

Additionally, as we have learned in medicine, the PKs of a drug may be affected by being taken on an empty stomach, interactions with other medications, or even the patient's own medical condition. As a pediatric intensive care unit physician, I often need to hold or change a patient's simple feeding regimens for several hours to prevent interference with a drug and its metabolism, or to not prolong a patient's QT interval. These issues are real and are unfortunately not addressed in this article.

Conclusion

The basis of this article is exciting and feasible in my opinion; however, I believe there many unanswered questions and assumptions that will affect the power and reliability of this study. Although I wish to honor and respect the time and energy that will go into this study, I also would like readers to recognize the high variability and small size of this study population.

References

1. Efron D, Taylor K, Payne JM, et al. Does cannabidiol reduce severe behavioural problems in children with intellectual disability? Study protocol for a pilot single-site I/II randomised placebo-controlled trial. *BMJ Open*. 2020;10(3):e034362.
2. Centers for Disease Control and Prevention. *Data and statistics on Down syndrome*. Updated December 5, 2019. Accessed July 7, 2002. http://www.cdc.gov/ncbddd/birthdefects/downsyndrome/data.html
3. Hunter J, Rivero-Arias O, Angelov A, Kim E, Fotheringham I, Leal J. Epidemiology of fragile X syndrome: a systematic review and meta-analysis. *Am J Med Genet A*. 2014;164A(7):1648-1658.
4. Bernstein BE, Pataki C, Glaze DG. Rett syndrome. Medscape. Updated February 20, 2020. Accessed July 7, 2020. https://emedicine.medscape.com/article/916377-overview#a3
5. Glaze DG, Schultz RJ. Rett syndrome: meeting the challenge of this gender-specific neurodevelopmental disorder. *Medscape Womens Health*. 1997;2(1):3.
6. Baio J. Prevalence of autism spectrum disorder among children aged 8 years – autism and developmental disabilities monitoring network, 11 sites, United States. *MMWR Surveill Summit*. 2014;63(SS02):1-21.
7. Vigli D, Cosentino L, Raggi C, Laviola G, Woolley-Roberts M, De Filippis B. Chronic treatment with the phytocannabinoid cannabidivarin (CBDV) rescues behavioural alterations and brain atrophy in a mouse model of Rett syndrome. *Neuropharmacology*. 2018;140:121-129.
8. Chakrabarti B, Persico A, Battista N, Maccarrone M. Endocannabinoid signaling in autism. *Neurotherapeutics*. 2015;12(4):837-847.
9. Devinsky O, Cross JH, Laux, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med*. 2017;376:2011-2020.
10. Gonçalves ECD, Baldasso GM, Bicca MA, Paes R, Capasso R, Dutra RC. Terpenoids, cannabimimetic ligands, beyond the cannabis plant. *Molecules*. 2020;25(7):1567.
11. Perucca E, Bialer M. Critical aspects affecting cannabidiol oral bioavailability and metabolic elimination, and related clinical implications. *CNS Drugs*. 2020 June 5. [online ahead of print]. doi:10.1007/s40263-020-00741-5