

Autism Spectrum Disorder and Cannabidiol: Have We Seen This Movie Before?

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Recently, the use of marijuana and cannabidiol (CBD) in children with autism spectrum disorder (ASD) has received increasing attention in the media with articles sensationally titled “Marijuana may be a miracle treatment for children with autism.”^{1,2} An absence of empirical data appears to have resulted in a growing body of anecdotal evidence espousing the benefits of CBD for children with ASD. Some reports describe the effects as miraculous or “unbelievable.”² Increasingly, parents of children with severe ASD, frustrated with the lack of options, have turned to CBD. Many have heard anecdotal reports of success; others have read of promising results with epileptic children. Parents who frequently felt they had exhausted all other options have turned to CBD as a “last resort.” An increasing number of parents are advocating for their children to be treated with CBD.³ Vocal parents have taken to the internet utilizing social media to distribute their message.⁴ However, clinical research remains nearly nonexistent.

History is laced with similar examples of parents and professionals attempting to help children with ASD. In 1998, Horvath and colleagues⁵ reported “dramatic improvement” in the behaviors of 3 children with ASD after intravenous administration of secretin, followed by renowned autism expert Bernard Rimland’s⁶ report on the behavioral, cognitive, and sensory improvements of a child who was administered secretin. On the basis of these first reports many parents of children with ASD pursued treatment with secretin, although secretin was not a proven, effective treatment and there was inadequate information about side effects. Since then, 16 randomized, placebo-controlled trials studying over 900 children have demonstrated a lack of evidence supporting that a single or multiple dose intravenous secretin is effective in improving the core symptoms of ASD (social and emotional reciprocity; restrictive, repetitive behaviors). Currently, secretin is not to be recommended as an evidence-based treatment for individuals with ASD.⁷

Another such example is hyperbaric oxygen therapy (HBOT). HBOT is a daily treatment where a patient enters

a hyperbaric chamber and the atmospheric pressure is increased well above sea level. Several small, uncontrolled case reports and case series reported some improvements in symptom scores in children with ASD who were treated with HBOT.⁸ Only one randomized controlled trial (RCT) reported effectiveness of this treatment,⁹ although the study has been criticized due to several methodological problems and those results have yet to be replicated.^{8,10} In 2017, the US Food and Drug Administration (FDA) issued warnings of legal action against several companies marketing unproven and potentially dangerous products and treatments for autism; HBOT as well as chelation therapies and detoxifying clay baths are included in these warnings.¹¹

This commentary provides guidance to clinicians who care for children with ASD. We identify the current level of evidence for the safe and effective use of CBD with children diagnosed with ASD and provide guidance for clinicians who encounter this population of children and families. The increasing popularity of the use of CBD for children with ASD as well as the history of failed examples of unproven products suggests a need to provide perspective and guidance on this topic.

Literature Support for Clinical Use

A review of the scientific literature was conducted for clinical evidence supporting the use of CBD for children with ASD utilizing MESH, PubMed, Medline, and Google Scholar. The search term “cannabidiol” paired with “autism” or “autism spectrum disorder” yielded limited results. Thus, the search parameter was broadened to include the terms “cannabis, endocannabinoids, cannabinoids, and marijuana” paired with autism or

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autism spectrum disorder. Despite the broadening of the search criteria, no clinical trials were found using these terms. The search did reveal one ongoing clinical study in Israel that is assessing the tolerability and efficacy of a CBD and tetrahydrocannabinol (THC) combination product in treating children with ASD. However, as this is an ongoing study no results are available yet.¹²

In contrast, there are indications for cannabis use that have more adequate literature support for its clinical utility. The 2018 report from the National Academy of Science, Engineering, and Medicine identified chronic pain, chemotherapy-induced nausea and vomiting, and spasticity associated with multiple sclerosis as areas with conclusive or substantial evidence of effect for cannabis use.¹³ These are disorders that primarily afflict the adult population. In pediatrics, the greatest evidence for cannabis use, specifically CBD, is for seizure disorders.

The role of cannabis in seizure disorders dates back thousands of years, yet it was not until recently that RCTs have demonstrated the safety and efficacy of cannabidiol using Epidiolex (oral cannabidiol).¹⁴⁻¹⁶ It is important to mention that it is estimated that 25% of children with treatment-resistant epilepsy have comorbid ASD. This can be more common in those with intellectual disability. Dravet syndrome and Lennox-Gastaut are 2 forms of treatment-resistant epilepsy that are associated with intellectual disability, and are commonly comorbid with ASD.¹⁷ This association is further supported by the coexistence of both epilepsy and ASD in individuals with Rett, Angelman, Dup15q, and Landau Kleffner syndromes.¹⁸ Thus, it is not surprising that studies conducted in the treatment-resistant epilepsy population have observed the potential benefit of CBD on behavioral symptoms of ASD.¹⁹

The US FDA urges caution when interpreting anecdotal reports of use of CBD in children with ASD. Manufacturing and testing standards and oversight of CBD products is absent. Testing of the chemical content of cannabinoid compounds in some products revealed many were found to not contain the levels of CBD they claimed to contain.^{20,21} Over the past several years, the FDA has issued multiple warning letters to firms that market unapproved new drugs that allegedly contain CBD and urged consumers “should beware purchasing and using any such products.”²¹ Currently, the only pharmaceutical grade CBD approved by the FDA is Epidiolex, which is indicated for the treatment of pediatric seizures associated with Lennox-Gastaut syndrome and Dravet syndrome.²²

Guidance for Physicians

Pediatricians and other clinicians are often left with a dilemma. The past several years has witnessed increasing

emphasis within the medical field on the importance of evidence-based decision making. Most agree that evidence is extremely important for researchers, practitioners, and policy makers charged with the task of making clinical decisions.²³ Recommendations in clinical practice are guided by the strength of scientific evidence on a topic. In most evidence hierarchies, current and well-designed RCTs and meta-analyses are at the top of the pyramid, and expert opinion and anecdotal experience are at the bottom.²⁴ RCTs are the strongest research design for establishing a cause-effect relationship while anecdotal evidence is extremely difficult to be independently replicated.²³ Although well established, RCTs provide the highest level of evidence for efficacy, and such studies addressing use of CBD in children with ASD may be difficult as they may involve ethical issues as well as technical problems (particularly with randomization, blinding, and safety in performing these studies).

Several authors suggest that medical professionals should take anecdotal reports seriously in their health care decisions.^{25,26} Our review did not reveal any case reports; only anecdotal reports by parents and other parties on the Internet. Failure to consider the quality of evidence can lead physicians to provide misguided recommendations. The strength of a recommendation reflects the extent to which we can be confident that desirable effects of CBD outweigh undesirable effects. Strong recommendations suggest most informed parents would likely choose the recommended treatment. Weak recommendations imply that a parent's choices will vary according to their beliefs and preferences.²⁶ As of today, the existing evidence does not support that CBD should be recommended as a treatment for ASD.

On the other hand, it may be ill-advised for physicians to merely inform parents there is no evidence to support the use of CBD for their child with ASD without further discussion. Parents may negatively perceive a physician's refusal to even discuss the use of CBD for their child or be disappointed with their doctor's lack of knowledge of the subject. Evanoffa and colleagues²⁷ reported that physicians in training in the United States felt unprepared to prescribe medical marijuana or answer questions regarding cannabis. The authors cited that only 9% of US medical schools have clinical cannabis content in their curricula.

Safety is another consideration in determining the use of any medicine or product. The World Health Organization and the National Institute on Drug Abuse at the National Institutes of Health agree that CBD is “generally well tolerated with a good safety profile” and studies have not identified any significant side effects.^{28,29} Even though the safety of pure CBD has been established, dosing for use in children with ASD

can be problematic. Studies are not only lacking to document the efficacy but also the proper dosing of CBD in this population. Many parents may embark on administration of CBD and will be challenged on how to assess or monitor what is appropriate dosing. The guidance of a qualified professional may not be able to overcome this obstacle.²⁵

Clinicians and parents are cautioned in interpreting claims reported on the Internet where motivations may be masked or covertly driven by incentives for profit. The CBD and medical cannabis market is estimated to generate \$4 billion in sales globally in 2018.¹ In the past “ethical problems that have arisen out of the interaction of pharmaceutical influences on clinical practice with human vulnerabilities when making decisions under conditions of uncertainty.”³⁰ CBD manufacturers stand to profit from the products they sell. Efforts to influence parents and consumers to buy their CBD products introduce a potential conflict of interest between the objective of maximizing profits and the need for individuals to receive the most safe and effective product at any given time. Discussions with families, and the child if appropriate, should involve informed decision making and address all the issues described above.

Below are guiding principles that may help frame the discussion.

1. Physicians who treat individuals with ASD should educate themselves about CBD. Although CBD and many complementary and alternative medicine (CAM) therapies lack proven effectiveness, physicians should recognize that the great majority of families of persons with ASD have tried at least one CAM approach.³¹ Parents who are interested in utilizing CBD for their child may be disappointed with their physicians’ lack of knowledge or negative attitudes about CBD and CAM in general.
2. Physicians can foster a trusting relationship by asking, in a nonjudgmental way, about CBD and listening to the parent’s perceptions regarding the benefits of CBD.
3. Once rapport and trust are established, the physician can help families distinguish validated, evidence-based treatment approaches from treatments that have been proven ineffective from those that are unproven and potentially harmful.
4. Clinicians should review the current state of evidence and safety with the parents and child.
5. Most physicians have received requests from patients for clinical recommendations. A strong recommendation for the use of CBD means that most informed parents would choose the

recommended management and that clinicians could structure their interactions with them accordingly. Weak recommendations suggest that parents’ choices will differ according to their values and preferences and clinicians should ensure that patients’ care is in keeping with their values and preferences.

6. Promoting informed decision making requires that parents and youth have adequate information and understanding about ASD and be aware of the choices and treatments available for their medical care, the potential outcomes of these choices and treatments, and have their personal values considered in decisions about their medical care.
7. Ultimately, a physician’s decision to utilize CBD in the management of children with ASD will be guided by the limited research findings, her or his clinical expertise and preference, as well as the parent’s values and wishes.

Conclusions

The use of CBD for clinical applications has gained increasing attention given its lack of psychoactive properties and potential benefits that have been noted in certain disease states, such as pediatric epilepsy and adult disorders. There is a paucity of literature supporting the clinical evidence for use of CBD in ASD. CBD and similar products remain a promising yet unproven intervention in the treatment of children with ASD. Instead, many questions remain unanswered. Will CBD be effective in the treatment of certain target symptoms in children with ASD? Will the selection of individuals who are candidates for this treatment be an important factor? What is the most appropriate ratio of CBD to THC for the beneficial effects, if any? Well-designed research studies are being planned and underway, but results have yet to emerge. However, in science the first principle is “one finding is no finding.” Thus, even if an initial RCT demonstrates benefits in utilizing CBD for children with ASD, there would still be a need for confirmation studies. We urge physicians to be familiar with the current state of the evidence, be able to have conversations with families and patients about the level of support, and be aware of the limitations that exist if choosing to recommend CBD as a treatment for children with ASD.

Author Contributions

CAS: Contributed to conception and design; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

DC: Contributed to conception and design; drafted manuscript; critically revised manuscript; gave final approval.


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References

- Kamin D. Is marijuana the world's most effective treatment for autism? *Newsweek*. <https://www.newsweek.com/2018/02/23/really-good-weed-why-cannabis-may-be-worlds-most-effective-remedy-core-806758.html>. Published February 15, 2018. Accessed April 8, 2018.
- Schwartz Y. Marijuana may be a miracle treatment for children with autism. *USA Today*. <https://www.usatoday.com/story/news/world/2017/04/25/marijuana-pot-treatment-children-autism-cannabis-oil/100381156/>. Published April 25, 2017. Accessed April 8, 2018.
- Abomary F. CBD autism therapy. *iDWeeds*. <https://idweeds.com/cbd-autism-treatment/>. Published March 2, 2017. Accessed April 8, 2018.
- Facebook, MAMMA USA. Mothers advocating medical marijuana for autism. <https://www.facebook.com/TexasMammas>. Accessed April 8, 2018.
- Horvath K, Stefanatos G, Sokolski KN, Wachtel R, Nabors L, Tildon JT. Improved social and language skills after secretin administration in patients with autistic spectrum disorders. *J Assoc Acad Minor Phys*. 1998;9:9-15.
- Rimland B. The autism-secretin connection. *Autism Res Rev Int*. 1998;12:3.
- Williams K, Wray JA, Wheeler DM. Intravenous secretin for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2012;(4):CD003495.
- Sakulchit T, Ladish C, Goldman RD. Hyperbaric oxygen therapy for children with autism spectrum disorder. *Can Fam Physician*. 2017;63:446-448.
- Rossignol D, Rossignol L, Smith S, et al. Hyperbaric treatment for children with autism: a multicenter, randomized, double-blind, controlled trial. *BMC Pediatr*. 2009;9:21.
- Jepson B, Granpeesheh D, Tarbox J, et al. Controlled evaluation of the effects of hyperbaric oxygen therapy on the behavior of 16 children with autism spectrum disorders. *J Autism Dev Disord*. 2011;41:575-588.
- US Food and Drug Administration. Autism: beware of potentially dangerous therapies and products [press release]. <https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm394757.htm>. Accessed November 15, 2018.
- Aran A. Cannabinoids for behavioral problems in autism spectrum disorder: a double blind, randomized, placebo-controlled trial with crossover. <https://clinicaltrials.gov/ct2/show/record/NCT02956226?id=NCT02956226&rank=1>. Accessed January 20, 2018.
- Abrams DI. The therapeutic effects of cannabis and cannabinoids: an update from the National Academies of Sciences, Engineering and Medicine report. *Eur J Intern Med*. 2018;49:7-11.
- O'Connell BK, Gloss D, Devinsky O. Cannabinoids in treatment-resistant epilepsy: a review. *Epilepsy Behav*. 2017;70(pt B):341-348.
- Thiele EA, Marsh ED, French JA, et al; GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2018;391:1085-1096.
- Devinsky O, Cross JH, Laux L, et al; Cannabidiol in Dravet Syndrome Study Group. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med*. 2017;376:2011-2020.
- He N, Li BM, Li ZX, et al. Few individuals with Lennox-Gastaut syndrome have autism spectrum disorder: a comparison with Dravet syndrome. *J Neurodev Disord*. 2018;10:10.
- Veliskova J, Silverman JL, Benson M, Lenck-Santini PP. Autistic traits in epilepsy models: why, when and how? *Epilepsy Res*. 2018;144:62-70.
- Anderson CLEV, DeMarse TB, Febo M, Johnson CR, Carney PR. Cannabidiol for the treatment of drug-resistant epilepsy in children: current state of research. *J Pediatr Neurol*. 2017;15:143-150.
- Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling accuracy of cannabidiol extracts sold online. *JAMA*. 2017;318:1708-1709.
- US Food and Drug Administration. Warning letters and test results for cannabidiol-related products [press release]. <https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm>. Accessed November 15, 2018.
- US Food and Drug Administration. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy [press release]. <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm611046.htm>. Published June 25, 2018. Accessed November 15, 2018.
- Puddy R, Wilkins N. *Understanding Evidence Part 1: Best Available Research Evidence. A Guide to the Continuum of Evidence of Effectiveness*. Atlanta, GA: Centers for Disease Control and Prevention; 2011. https://www.cdc.gov/violenceprevention/pdf/understanding_evidence-a.pdf. Accessed November 15, 2018.
- Hoffman T, Bennett S, Del Mar C. *Evidence-Based Practice Across the Health Professions*. 2nd ed. Chatswood, New South Wales, Australia: Elsevier; 2013.
- Kossen J. How does cannabis consumption affect autism? *Leafly*. <https://www.leafly.com/news/health/how-does>

- cannabis-consumption-affect-autism. Published May 19, 2016. Accessed November 15, 2018.
26. Grinspoon L. A novel approach to the symptomatic treatment of autism. *O'Shaughnessy's*. <http://www.beyondthc.com/wp-content/uploads/2013/08/GrinspoonAutism.pdf>. Published 2010. Accessed April 8, 2018.
 27. Evanoffa AB, Quan T, Dufault C, Awad M, Bierut LJ. Physicians-in-training are not prepared to prescribe medical marijuana. *Drug Alcohol Depend*. 2017;180:151-155.
 28. World Health Organization. Cannabidiol (CBD). Pre-review report. Agenda item 5.2. http://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf. Published November 2017. Accessed November 15, 2018.
 29. Volkow N. Cannabidiol: barriers to research and potential medical benefits. <https://suziespettreats.com/news/cannabidiol-barriers-research-potential-medical-benefits/>. Published June 24, 2015. Accessed November 15, 2018.
 30. Haque O, De Freitas J, Bursztajn H, et al. The ethics of the pharmaceutical industry influence in medicine. <http://www.unesco-chair-bioethics.org/wp-content/uploads/2015/09/The-Ethics-of-Pharmaceutical-Industry-Influence-in-Medicine.pdf>. Published May 2013. Accessed April 8, 2018.
 31. Hopf KP, Madren E, Santianni KA. Use and perceived effectiveness of complementary and alternative medicine to treat and manage the symptoms of autism in children: a survey of parents in a community population. *J Altern Complement Med*. 2016;22:25-32.