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# Little is known about cannabidiol for improving severe behavioral symptoms of autistic spectrum disorder

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**ABSTRACT** A clinical decision report appraising Barchel D, Stolar O, De-Haan T, et al. Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and co-morbidities. *Frontiers in Pharmacology.* 2019;9. https://doi.org/10.3389/fphar.2018.01521.

***Keywords***: *autism, cannabidiol, behavioral symptoms*

## Clinical Context

Hunter Walker (pseudonym) is a 9-year old boy presenting to the neurology clinic for follow-up for controlled focal motor seizures, developmental delay, cerebral palsy, and autism spectrum disorder (ASD) with severe behavioral symptoms. His current medication regime includes clobazam and lacosamide. His mother is having a lot of trouble managing his behavior at home. While in clinic, we noticed how Hunter would run around, play with faucets, close doors, and constantly be on the move. Ms. Walker also has four other children at home, and Hunter cannot stay in school for too long because of his disruptive behavior. Hunter has constant restlessness, hyperactivity, and frequent rage attacks. Ms. Walker has very little social support, with no nearby family or other parental contribution for raising Hunter; she quit her job in order to care for Hunter. Ms. Walker does have a friend who has been successful in managing her son's ASD behavioral outbursts with cannabidiol oil. The recommendation of the pediatric neurologist was risperidone, as that has been one of the first line medication for treatment of behavioral symptoms in ASD.[1] Ms. Walker was hesitant to add another medication and insists on trying something more "natural." She comes to us for our professional opinion on cannabidiol oil use in ASD.

## Clinical Question

Is cannabidiol oil effective in decreasing disruptive behavioral symptoms of ASD?

## Research Article

Barchel D, Stolar O, De-Haan T, et al. Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and co-morbidities. *Frontiers in Pharmacology.* 2019;9. https://doi.org/10.3389/fphar.2018.01521.

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## Related Literature

PubMed was searched using the terms “cannabis OR cannabidiol” AND “autism OR autistic spectrum disorder”. This yielded 57 articles. Screening of the articles by reading the titles and abstracts resulted in 19 papers relevant to the clinical scenario. Of those 19, ten articles were literature reviews regarding the treatment of autism with cannabis derived products.[2-11] The remaining nine articles consisted of a viewpoint, ethics statement, letter, two studies done on adult populations, and four studies done using cannabis-based products for the treatment of autism related symptoms in children.[12-20]

The 2019 Schleider et al. article was about a prospective study looking at the safety and efficacy of medical cannabis treatment in children with ASD.[17] A CBD:THC solution of 30% to 1.5% was used in 188 children with ASD who had comorbid behavioral symptoms. Treatment effectiveness was assessed at 6 months via a questionnaire provided to the caregivers. While this study matches the clinical scenario well, the main limitation is that it does not focus on how and what types of behavioral symptoms were improved. Another limitation was that a variety of percentages were used for the CBD:THC solutions.

Fleury-Teixeira et al conducted an observational study that looked at the effect on behavioral symptoms in 18 children with ASD after using a cannabis sativa extract (CBD:THC ratio of 75:1) .[18] The authors measured treatment effect via a monthly questionnaire assessing behavioral improvements. This study design is not ideal and the population size is a concern, even though it matches our clinical scenario.

Aran et al published a brief report in 2019 as a retrospective feasibility study for treating children with ASD with cannabidiol.[19] Their sample consisted of 60 children with ASD and severe behavioral problems who received treatment (CBD:THC of 20:1). Improvements were assessed by a questionnaire filled out by the parents. This population matches our clinical scenario well, but it does not focus on specific behavioral improvements.

Barchel et al published a study in 2019 regarding cannabidiol use in children with ASD to help treat related symptoms and co-morbidities.[20] This study consisted of 53 children who were treated with cannabidiol oil (CBD:THC of 20:1). The researchers conducted telephone interviews on a biweekly basis for follow up and reported the change in each behavioral symptom and comorbidity separately, along with overall change. It did not focus on or discuss safety of treatment. This paper is not the ideal study design, but the population, intervention, outcomes, and clinical question match Ms. Walker’s concerns. This is the most appropriate paper. The Grade of Recommendation using the SORT criteria is C—small, poorly designed studies to guide clinician opinion.[21]

## Critical Appraisal

The study was conducted in Israel with children diagnosed with ASD based on DSM IV or V criteria. The primary outcome was symptom change, focusing on patient-oriented outcomes. It fits level 3 evidence using the SORT criteria.[21] The inclusion criteria were children diagnosed with ASD who had never used any cannabis products before. Exclusion criteria was not specifically stated, but some patients were excluded because they were treated for less than 30 days. Parents of the child received a license to use cannabidiol oil solution that was prepared by the Tikun Olam company and had a concentration of 30% and a 1:20 ratio of cannabidiol and THC. The daily dose for the cannabidiol and THC was 16 mg/kg and 0.8 mg/kg respectively. The ASD comorbid symptoms evaluated were hyperactivity, sleep issues, self-injury, and anxiety. Symptom change was graded as improvement, no change, or worsening. A biweekly follow-up phone interview was conducted to assess the child’s change in symptoms, adverse side effects, and any medications used.

Fifty-three children (95% male, average age of 11 years) were included in this study, but two families missed providing reports. The minimum time for follow up was 31 days and maximum was 588 days. The two most common symptoms experienced by this population were hyperactivity and self-injurious behavior (both at 88.7%), followed by sleep disturbances (54.7%). Anxiety (49.1%) and social communication deficits (41.5%) were the remaining two symptoms. The grading of improvement in symptoms was based off of published data that used conventional treatments. For example, an improvement in hyperactivity would have to be that 80% or more of the hyperactivity symptoms have decreased. A number of patients were taking additional medications, including atypical antipsychotics (58.4%), antiepileptics (15%), typical antipsychotics (11.3%), and stimulants (9.4%). The authors did not control for this, as these medications were what the children were taking prior to starting the study.

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Overall improvement of ASD comorbidities was reported by 74.5%. Of the 38 children with hyperactivity symptoms, 68.4% reported improvement. Although there was a large amount of improvement, it was not statistically significant when compared to the conventional treatment (p = 0.125). There was marginal significance in improvement in the 34 children with self-injurious behavior (67.6%) when compared to conventional treatment (p = 0.063). No significant difference in the improvement of sleep and anxiety were found, but there was improvement recorded in 71.4% (21 reports) and 47.1% (17 reports) of patients respectively. The most common adverse side effects were somnolence and change in appetite, but they were mild.

One limitation of this study is that it is not a randomized, placebo-controlled trial, so it is difficult to isolate what caused the improvement in symptoms. There was just one cohort of children, all taking the same formula with no control group, and this makes it difficult to determine if the treatment worked or not. All the results might be explained by the placebo effect and there was a ahigh risk of bias because of the self-report nature of the outcome of interest. These children were also on other medications, so this means that the cannabidiol may not have been the only factor that led to improvement or non-improvement in these children. There are several ongoing clinical trials studying CBD oil and ASD symptoms, but with no reports published yet, this makes the Barchel et al study the best and only one available. Another limitation is the small sample size, which could make it difficult to apply the results to the general population. A third source of bias is that these children were on other medications, making it hard to tell if CBD caused the improvement or if there were other medication effects. One final limitation to consider is that ASD can be divided up into levels of severity of disease based on how much support a child needs and so, this study does not distinguish between ASD levels. Some children that require a lot of support may need a longer duration or stronger dose of treatment for improvements to be seen.

Despite these potential sources of bias, this study showed a trend toward improvement in controlling hyperactivity, self-injurious behavior, anxiety, and sleep disturbances with CBD oil through observation and anecdotal evidence.

## Clinical Application

The use of cannabidiol oil for ASD symptoms is an ongoing area of investigation. Several studies are underway to determine the formulation, dosage, and effect of CBD oil in children with autism.[22-24] Currently in the United States, CBD oil is only approved by the FDA for treatment of seizures due to certain syndromes.[25]

Hunter is a child who suffers from controlled focal motor seizures, developmental delay, cerebral palsy, and ASD with symptoms of hyperactivity and self-injurious behavior. This study showed an improvement in these ASD symptoms through anecdotal and observational evidence. However, some of the children in the study reported side effects, mainly somnolence and changes in appetite. We discussed the benefits and risks of adverse effects of the therapy based on the available evidence with Ms. Walker. In addition, we discussed that we cannot prescribe a dose for CBD oil because it is only approved for seizures. Ms. Walker was also made aware that these improvements were not significant when compared to traditional pharmacotherapy. She was overall exhausted with Hunter's daily symptoms and was insistent on trying anything that helped. She decided to try the CBD oil on her own through a medical marijuana license. After a thorough discussion about being cautious when using unapproved CBD oils, Ms. Walker finalized her choice. She wanted Hunter to have an improvement in his symptoms and saw hope in this treatment. Unfortunately, there was a lack of follow-up with Ms. Walker to see how Hunter was doing.

## New Knowledge Related to Clinical Decision Science

Ms. Walker's situation is not a unique one. There are many families who struggle to balance children with chronic medical conditions with work and daily family responsibilities. It is common that parents hear from other parents about different remedies or medications. Indeed, physician parents have been known to give their normal children diphenhydramine to calm a child in far less overwhelming situations. We as providers, try to make an informed and justified recommendation based on research. In this case, CBD may have been helpful for Hunter, but there was no evaluation of safety and the one study that was discussed was lacking a significant enough population to solidify an answer. Overall, it was Ms. Walker's frustration and questioning that led us to investigate this in the first place. As is often the case, treating the caregiver's stress ICD-10: Z74.8 (Other problems related to care provider dependency) is probably the best way to help Hunter. Viewed with this perspective, it would be interesting to contemplate

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a study where both the caregiver and the child with autism / behavioral disturbance are both treated with CBD-THC, Given that in many states cannabis is legal, physicians might actually be seeing that type of case now and not be aware of it.

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