2022 Qualifying Condition Form

Upon petition, the State Medical Board of Ohio has the authority to approve and designate conditions or diseases as qualifying medical conditions for treatment with medical marijuana. For the calendar year of 2022, the board will accept petitions for consideration between November 1, 2022 and December 31, 2022.

The following conditions are already part of the program: AIDS, amyotrophic lateral sclerosis, Alzheimer's disease, cachexia, cancer, chronic traumatic encephalopathy, Crohn's disease, epilepsy or another seizure disorder, fibromyalgia, glaucoma, hepatitis C, Huntington's disease, inflammatory bowel disease, multiple sclerosis, pain that is either chronic and severe or intractable, Parkinson's disease, positive status for HIV, post-traumatic stress disorder, sickle cell anemia, spasticity, spinal cord disease or injury, terminal illness, Tourette syndrome, traumatic brain injury, and ulcerative colitis.

The board's Medical Marijuana Committee determined that the following are considered to be covered by an existing qualifying condition.

- Arthritis (determined to be covered by pain that is either chronic or intractable, February 2021)
- Chronic Migraines (determined to be covered by pain that is either chronic or intractable, February 2021)
- Complex Regional Pain Syndrome (determined to be covered by pain that is either chronic or intractable, February 2021)
- Degenerative Disc Disease (determined to be covered by pain that is either chronic or intractable, February 2022)
- Lupus where pain is present (determined to be covered by pain that is either chronic or intractable, February 2022)

You do not need to submit a petition for any of these conditions. Click here to read the board's position statement.

The petition will not be considered if:

- Received after December 31, 2022
- It seeks to add a broad category of diseases or conditions
- The condition that has been previously reviewed by the board and rejected unless new scientific research that supports the request is offered

If you are petitioning for a previously considered condition:

- Do not resubmit documents which have already been reviewed by the board
- Only new scientific research should be submitted for previously rejected petitions
- A catalogue of submitted research and documents can be found here

Most information submitted as part of a petition is public record and may be posted on the Medical Board's website at med.ohio.gov. This includes the submitter's name provided contact information, and responses.

Instructions:

- All sections below are required to be completed per Ohio Administrative Code 4731-32. All text boxes are required. Applicants may type "see attached" or "previously submitted" in the required fields.
- If you would like for the Medical Board to consider multiple conditions, please complete a separate submission for each one.
- Please refrain from providing personal medical information as all submissions are subject to public record requests.

First Name *	Last Name *	Email *
Charles	Trefny	charlie.trefny@ohiomcia.com
Address *	City *	State *
140 E. Town Street	Columbus	OHIO
Zip Code *	County *	Specific Disease or Condition *
43215	FRANKLIN	Autism Spectrum Disorder

1) Information from experts who specialize in the disease or condition *

Attached.

Please do not include any links in the text field. All materials submitted for review must be attached in the format of a Microsoft Word document or PDF

Question 1 Attachments

File Name	Size
ASD 2022 Petition Part 1.pdf	187.42 kB

Links will not be reviewed

2) Relevant medical or scientific evidence pertaining to the disease or condition *

Attached.

Please do not include any links in the text field. All materials submitted for review must be attached in the format of a Microsoft Word document or PDF

Question 2 Attachments

File Name	Size
ASD 2022 Petition Part 2.pdf	196.07 kB

3) Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition *

Attached.

Please do not include any links in the text field. All materials submitted for review must be attached in the format of a Microsoft Word document or PDF

Question 3 Attachments

File Name	Size
ASD 2022 Petition Part 3.pdf	194.89 kB

4) Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation *

Attached.

Please do not include any links in the text field. All materials submitted for review must be attached in the format of a Microsoft Word document or PDF

Question 4 Attachments

File Name	Size
ASD 2022 Petition Part 4.pdf	199.64 kB
Cannabidiol in Treatment of Autism Spectrum Disorder.pdf	100.39 kB
Cannabis and cannabinoid use in autism spectrum disorder a systemic review.pdf	245.19 kB
Safety and Efficacy of Medical Cannabis in Autism Spectrum Disorder Compared with Commonly Used Medications 2022.pdf	253.90 kB
Medical cannabis for the treatment of comorbid symptoms in children with autism spectrum disorder An interim analysis of biochemical safety.pdf	716.47 kB
Real Life Experience of Medical Cannabis Treatment in Autism 2019.pdf	856.84 kB
HB60 Raymond Chandler Proponent.pdf	1.05 MB

5) Letters of support provided by physicians with knowledge of the disease or condition. This may include a letter provided by the physician treating the petitioner, if applicable. *

Attached.

Please do not include any links in the text field. All materials submitted for review must be attached in the format of a Microsoft Word document or PDF

Question 5 Attachments

File Name	Size
ASD 2022 Petition Part 5.pdf	201.11 kB

1. **Information from experts who specialize in the disease or condition:**

Autism Spectrum Disorder

The Mayo Clinic defines Autism spectrum disorder as a condition related to brain development that impacts how a person perceives and socializes with others, causing problems in social interaction and communication. The disorder also includes limited and repetitive patterns of behavior. The term "spectrum" in autism spectrum disorder refers to the wide range of symptoms and severity.

Autism spectrum disorder begins in early childhood and eventually causes problems functioning in society — socially, in school and at work, for example. Often children show symptoms of autism within the first year. A small number of children appear to develop normally in the first year, and then go through a period of regression between 18 and 24 months of age when they develop autism symptoms.

While there is no cure for autism spectrum disorder, intensive, early treatment can make a big difference in the lives of many children.

Some children show signs of autism spectrum disorder in early infancy, such as reduced eye contact, lack of response to their name or indifference to caregivers. Other children may develop normally for the first few months or years of life, but then suddenly become withdrawn or aggressive or lose language skills they've already acquired. Signs usually are seen by age 2 years.

Each child with autism spectrum disorder is likely to have a unique pattern of behavior and level of severity — from low functioning to high functioning.

Some children with autism spectrum disorder have difficulty learning, and some have signs of lower than normal intelligence. Other children with the disorder have normal to high intelligence — they learn quickly, yet have trouble communicating and applying what they know in everyday life and adjusting to social situations.

Because of the unique mixture of symptoms in each child, severity can sometimes be difficult to determine. It's generally based on the level of impairments and how they impact the ability to function.

2. Relevant medical or scientific evidence pertaining to the disease or condition:

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by sustained social impairments in reciprocal social communication and interactions; and repetitive behaviors, interests, or activities (American Psychiatric Association 2013). These essential markers of autism spectrum disorder present in early childhood and limit everyday functioning (American Psychiatric Association 2013). The word "spectrum" is used to define ASD since the disorder manifests itself in diverse ways, depending on varying symptom severity, the individual's developmental level, and chronological age (American Psychiatric Association 2013).

To be diagnosed with ASD, a person needs to fulfil the following criteria (American Psychiatric Association, 2013):

1) Persistent deficits in social communication and interaction across multiple contexts, as demonstrated by all of the following:
   a) Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and inability to have normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
   b) Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
   c) Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
   d) (These criteria can be currently occurring or have occurred in the patient's past. Examples are illustrative, not exhaustive.)
2) Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following:
   a) Stereotyped or repetitive motor movements, use of objects, or speech (e.g., repetitive hand flapping, lining up toys or flipping objects, delayed or immediate parroting of others' speech, idiosyncratic phrases).
   b) Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
   c) Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., a child who is extremely attached to a spoon, an adult who spends hours rewriting specific phrases).
   d) Extremely exaggerated or dulled reactions to sensations or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
   e) (These criteria can be currently occurring or have occurred in the patient's past. Examples are illustrative, not exhaustive.)

3) Symptoms must be present in the early developmental period. Though, symptoms may not become fully apparent until social demands exceed limited capacities. Symptoms may also be masked by learned strategies in later life.
4) Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
5) These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur. Social communication should be below what is expected for general developmental level, in order to make comorbid diagnoses of autism spectrum disorder and intellectual disability.

3. **Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition:**

According to the CDC there are no medications that treat the core symptoms of ASD. Some medications treat co-occurring symptoms that can help people with ASD function better. For example, medication might help manage high energy levels, inability to focus, or self-harming behavior, such as head banging or hand biting. Medication can also help manage co-occurring psychological conditions, such as anxiety or depression, in addition to medical conditions such as seizures, sleep problems, or stomach or other gastrointestinal problems.

Because no cure exists for autism spectrum disorder, and there is no one-size-fits-all treatment. The goal of treatment is to maximize ability to function by reducing autism spectrum disorder symptoms and supporting development and learning.

Treatment options may include:

- Behavior and communication therapies. Many programs address the range of social, language and behavioral difficulties associated with autism spectrum disorder. Some programs focus on reducing problem behaviors and teaching new skills. Other programs focus on teaching children how to act in social situations or communicate better with others. Applied behavior analysis (ABA) can help children learn new skills and generalize these skills to multiple situations through a reward-based motivation system.
- Educational therapies. Children with autism spectrum disorder often respond well to highly structured educational programs. Successful programs typically include a team of specialists and a variety of activities to improve social skills, communication, and behavior. Preschool children who receive intensive, individualized behavioral interventions often show good progress.
- Family therapies. Parents and other family members can learn how to play and interact with their children in ways that promote social interaction skills, manage problem behaviors, and teach daily living skills and communication.
- Other therapies. Depending on your child's needs, speech therapy to improve communication skills, occupational therapy to teach activities of daily living, and physical therapy to improve movement and balance may be beneficial. A psychologist can recommend ways to address problem behavior.
- Medications. No medication can improve the core signs of autism spectrum disorder, but specific medications can help control symptoms. For example, certain medications may be prescribed if your child is hyperactive; antipsychotic drugs are sometimes used to treat severe behavioral problems; and antidepressants may be prescribed for anxiety. Keep all health care providers updated on any medications or supplements your child is taking. Some medications and supplements can interact, causing dangerous side effects.

4. **Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer reviewed studies, and other type of medical or scientific documentation.**

This past General Assembly, Ohio's legislature took up the issue of adding Autism spectrum disorder (ASD) to the list of qualifying conditions for Ohio's Medical Marijuana Control Program. H.B. 60 was introduced back in February of 2021, was passed by the House with an overwhelming majority 77-17 vote, and ultimately died in the Senate where it only received one hearing. However, throughout this process extremely convincing testimony was heard by the Ohio House Health Committee, attached to this section is testimony from one of the many who found medical cannabis to be the best treatment for there symptoms from Autism spectrum disorder (HB 60 Raymond Chandler Proponent).

Autism has been approved as a condition for medical marijuana in 16 states and Puerto Rico. Eight other states and Washington D.C. have indirectly approved autism by allowing a physician to use their professional discretion to approve any condition that may benefit from medical marijuana.

In states where autism is an approved condition, only a small percentage ranging from 0.1% - 2% of the patient population is registered under autism.

The studies summarized below highlight effective use of medical cannabis as treatment for those debilitated by symptoms of the disorder (studies attached):

Cannabidiol in Treatment of Autism Spectrum Disorder: A Case Study, Lucy Ma, Sofia Platnick, Howard Platnick, 2022

This case study aimed to demonstrate the use of cannabidiol (CBD) with low-dose tetrahydrocannabinol (THC) in managing symptoms associated with autism spectrum disorder (ASD) to increase the overall quality of life for these individuals and their families.

This case concluded that the use of cannabidiol in the treatment of Autism spectrum disorder should be considered as an option in managing symptoms related to autism.

In the case study presented, the child patient has shown behavioral and cognitive improvements with no side effects reported. In this case, the child patient responded positively to the introduction of CBD oil treatment with reduced negative behaviors, better sleep, and improved communication.

Cannabis and cannabinoid use in autism spectrum disorder: a systematic review, Estácio Amaro da Silva Junior, Wandersonia Moreira Brito Medeiros, Nelson Torro, João Marçal Medeiros de Sousa, Igor Bronzeado Cahino Moura de Almeida, Filipe Barbosa da Costa, Katiúscia Moreira Pontes, Eliane Lima Guerra Nunes, Marine Diniz da Rosa, Katy Lísias Gondim Dias de Albuquerque, 2022

This study carried out a systematic review of studies that investigated the clinical effects of cannabis and cannabinoid use on ASD, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA checklist).

The study concluded that cannabis and cannabinoids may have promising effects in the treatment of symptoms related to ASD and can be used as a therapeutic alternative in the relief of those symptoms.

Medical cannabis for the treatment of comorbid symptoms in children with autism spectrum disorder: An interim analysis of biochemical safety, Orit Stolar, Ariela Hazan, Roni Enten Vissoker, Ibrahim Abu Kishk, Dana Barchel, Mirit Lezinger, Adi Dagan, Nir Treves, David Meiri, Matitiahu Berkovitch, Elkana Kohn and Eli Heyman, 2022

Questions have arisen regarding the safety of medical cannabis used to treat children and adolescents with ASD, the aim of the above study was to assess the safety of a CBD-rich oil treatment and the study found that CBD-rich cannabis oil (CBD: THC 20:1), appears to have a good safety profile.

Safety and Efficacy of Medical Cannabis in Autism Spectrum Disorder Compared with Commonly Used Medications, Richard Holdman, Daniel Vigil, Kelsey Robinson, Puja Shah, Alexandra Elyse Contreras, 2022

Further evidence to the safety and efficacy of medical cannabis utilized for symptoms of ASD compared with commonly used medications was presented by this study which aimed to evaluate the safety and efficacy of medications commonly used in autism spectrum disorder (ASD) and compare this to what current research has shown regarding medical cannabis use in this population. The study found that CBD-rich medical cannabis seems to be an effective, tolerable, and relatively safe option for many symptoms associated with ASD.

Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy, Lihi Bar-Lev Schleider, Raphael Mechoulam, Naama Saban, Gal Meiri, & Victor Novack, 2019

This study showed that cannabis in ASD patients appears to be well tolerated, safe and an effective option to relieve symptoms associated with ASD from data prospectively collected as part of the treatment program of 188 ASD patients treated with medical cannabis between 2015 and 2017.

With ample evidence supporting improved quality of life for persons living with ASD, along with the evidence cannabis has shown to be an effective treatment for symptoms relating to autism spectrum Disorders the OMCIA urges the State Medical Board to approve ASD as a qualifying condition to Ohio's Medical Marijuana Control Program. Based upon personal testimony shared with Ohio's legislature and the studies provided in this section there is little doubt that if persons with ASD and their support team strategically work with their physician teams and healthcare professionals, medical cannabis is a safe alternative treatment option.

Cureus

Open Access Case Report

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Cannabidiol in Treatment of Autism Spectrum Disorder: A Case Study

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Abstract

This case study aims to demonstrate the use of cannabidiol (CBD) with low-dose tetrahydrocannabinol (THC) in managing symptoms associated with autism spectrum disorder (ASD) to increase the overall quality of life for these individuals and their families. ASD is a neurodevelopmental disorder affecting cognitive development, behavior, social communication, and motor skills. Despite the increasing awareness of ASD, there is still a lack of safe and effective treatment options. The study includes a nine-year-old male patient who was diagnosed with nonverbal ASD. He exhibited emotional outbursts, inappropriate behaviors, and social deficits including challenges in communicating his needs with others. Since the patient was unable to attain independence at school and at home, his condition was a significant burden to his caregivers. The patient was treated with full-spectrum high CBD and low THC oil formulation, with each milliliter containing 20 mg of CBD and <1 mg of THC. CBD oil starting dose was 0.1ml twice daily, increased every three to four days to 0.5ml twice daily. Overall, the patient experienced a reduction in negative behaviors, including violent outbursts, self-injurious behaviors, and sleep disruptions. There was an improvement in social interactions, concentration, and emotional stability. A combination of high CBD and low-dose THC oil was demonstrated to be an effective treatment option for managing symptoms associated with autism, leading to a better quality of life for both the patient and the caregivers.

Categories: Neurology, Pediatrics, Psychiatry
Keywords: psychiatry, child and adolescent psychiatry, pediatrics neurology, alternate therapy, cannabis (marijuana), tetrahydrocannabinol (thc), cannabidiol (cbd), adolescent cannabis use, autism spectrum disorder (asd), autism spectrum disorder and anxiety disorder

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in communication, social interactions, restricted interests, and repetitive behaviors [1]. ASD is associated with medical conditions such as epilepsy and deficiency in intellectual abilities [1]. The World Health Organization (WHO) estimates that one in 100 children is diagnosed with autism worldwide [2]. However, the epidemiology can vary greatly depending on geographic location. For example, the Public Health Agency of Canada reports ASD prevalence of one in every 50 Canadian children [3].

The WHO Quality of Life Instrument, Short Form (WHOQOL-BREF) developed by the WHO to effectively measure the experience of individuals with ASD, has shown that associated medical conditions negatively impact the individual's quality of life [4]. Those with ASD, as well as their families, experience a great deal of stress and disruption with this diagnosis. Most individuals with autism will not live independently or become employable; the majority of individuals will require lifelong, primary support [5]. Families experience ongoing challenges that can affect the quality of life, including health-related factors, financial barriers, number of children, and parental stress [5]. More than 70% of those with autism suffer from comorbid conditions, most commonly anxiety, depression, and attention deficit and hyperactivity disorder (ADHD) [6]. Researchers have explored both genetic and environmental factors that influence the development of the brain and its correlation with ASD risks, such as exposure to lead, ethyl alcohol, and methyl mercury [7].

The objective of this case study is to demonstrate the use of cannabidiol (CBD) in a full-spectrum formulation, with low-dose tetrahydrocannabinol (THC), as a treatment option for managing symptoms associated with ASD to increase the overall quality of life for these individuals and their families. The patient in the case presented resides in Canada, where both medical and recreational cannabis are legal in all forms.

Case Presentation

The nine-year-old patient (weight 39 kilograms) was diagnosed with nonverbal ASD when he was three years old and required 24-hour supervision. He had a comorbid diagnosis of insulin-dependent diabetes mellitus (Type I diabetes), which required daily insulin injections. The patient had mild asthma with infrequent use of a salbutamol puffer. Otherwise, he was on no other medications. Due to cultural and

personal preferences, the patient's mother declined to use psychiatric medications.

Prior to initiating CBD treatment, the patient exhibited behavioral symptoms with outbursts of anger and physical aggression (punching, kicking, biting, head-butting, and scratching). He required daily insulin injections, which were accompanied by self-injurious actions including head and chest punching. The patient displayed inappropriate behaviors such as playing with feces and rocking on the floor for self-soothing (stimming). He was constantly frustrated by misunderstandings when interacting with others, as he was unable to express his needs verbally. He had difficulty with sleep initiation, taking one to four hours to fall asleep and sleeping a total of four to five hours a night with frequent awakening. He required pull-up diapers each night due to incontinence. The patient attended public school with support and struggled to perform well academically. There were difficulties interacting with the teachers and other students, and following rules.

The patient began CBD treatments through a medical cannabis clinic at age 7.5 years starting with full-spectrum high CBD and low THC oil formulation. The carrier oil is a medium chain triglyceride (MCT) coconut extract, an industry-standard formulation [8]. Each milliliter has 20 mg of CBD and < 1 mg of THC. The starting dose was 0.1 ml two times daily with meals and this was increased every three to four days until it reached a therapeutic response or 0.5ml two times a day.

Within the first two weeks of starting treatment, the patient was able to fall asleep in 10-15 minutes and sleep for 8-10 hours. He stopped wearing pull-up diapers as he was able to go to the washroom, wash his hands, and go back to bed without supervision, demonstrating a new behavior. There was reduced anxiety contributing to improved mood and concentration. He was able to practise gripping his pencil and trace letters. He started to follow simple instructions, such as retrieving three separate clothing items. At school, the patient received report cards with better grades and experienced less anger. This improvement allowed him to interact with his peers without signs of aggression. The patient's mother stated, “Since starting CBD, teachers and (the) principal have noted significant positive changes. He sits for over 30 minutes, holds a marker, and is focused enough to try and trace letters or numbers. The change has been amazing for us to witness.”

After initiating CBD, there was a significant reduction in overeating and “grazing” as the patient was content with regular meal intervals. His weight did not change significantly, aside from the expected increase with maturation (current weight 52 kilograms). Self-injurious and violent behaviors diminished with treatment, which allowed for easier administration of his daily insulin injections. Table *1* provides a comparison between the patient’s behaviors and characteristics before and after initiating CBD treatment.

Prior to CBD Treatment	After CBD Treatment
HbA1C: 9-10% range*	HbA1C: 8-9% range
Self-injurious behaviors	Minimal self-injurious behaviors
Inappropriate behaviors	Reduced inappropriate behaviours
Difficulty communicating verbally	Followed simple instructions
Poor sleep time and quality (4-5 hours per night)	Improved sleep time and quality (8-10 hours per night)
Poor academic performance	Improved academic performance
2-4 hours in sensory room at school	30 minutes/day in sensory room at school
Irregular eating pattern (grazing)	Regular meal intervals

TABLE 1: A comparison of characteristics before and after initiating CBD treatment for the patient in the case presented

*(normal HbA1C < 5.7% and diabetic > 6.7% with treatment goal of < 7%)

CBD: cannabidiol; HbA1C: hemoglobin A1c

The patient did not have access to the CBD for seven days while on a family trip, and his behavior regressed to pre-treatment levels. Within 24 hours, the patient experienced insomnia. After four hours, he was able to fall asleep although it was described as intermittent and fitful. After two days, there was a reduction in verbal communication and response to verbal cues, and he stopped following simple instructions. On the third day, the patient resumed self-injurious behavior. Upon returning home and restarting treatment, his

sleep was regulated within two days. In the following two days, the patient regained his verbal capacity and concentration, resulting in a decrease in self-injurious behaviors.

To match physical growth, the CBD dose was later increased to 0.5ml three times a day with continued positive results including further improvement in communication and a further decline in aggressive behaviors (the upper limit prescribed was 1 ml three times a day). The caregiver did not report any side effects with the cannabidiol treatment.

Discussion

Conventional medical treatments such as atypical antipsychotics and selective serotonin reuptake inhibitors are used to reduce or eliminate behavioral symptoms [9]. However, these psychotropic drugs may lead to side effects such as nephropathy, hepatopathy, and metabolic syndromes [9]. Of children with autism and behavioral symptoms, 40% do not respond well to standard treatments, which motivates researchers to search for alternative pharmacological treatments, including substances derived from Cannabis sativa [10]. The use of CBD as a pharmacological treatment has been shown to relieve spasticity, pain, sleep disorders, seizures, and anxiety [10]. CBD affects the brain by interacting with the endocannabinoid system to modulate cognition, socioemotional responses, susceptibility to seizures, and nociception [11].

The endocannabinoid system consists of two identified receptors: CB1 and CB2 [11]. THC is the major psychoactive component of the cannabis plant, which interacts with both the CB1 and CB2 receptors [12]. CB1 receptors are found most commonly in the central nervous system (CNS), where THC interacts with the CB1 receptors to modulate neuronal excitability to produce psychotropic effects or “feeling high”. CB2 receptors are found primarily in microglia and vascular elements, such as in the circulating immune cells, spleen, and peripheral nerve terminals. Together, the endocannabinoid system is able to modulate emotional responses, mood, pain levels, immune system, and social behaviors [12].

Two endogenous cannabinoids identified are N-arachidonoylethanolamine (anandamide) and two arachidonoylglycerol (2-AG) [13]. These endocannabinoids are enzymes that have the ability to activate the CB1 and CB2 receptors [11]. Anandamide is a major endocannabinoid that has reduced levels in patients with ASD [13]. CBD acts as an inhibitor of fatty acid amide hydrolase (FAAH), which can break down anandamide, thereby increasing available anandamide levels [14]. By a similar mechanism, CBD reduces MAGL-mediated degradation of 2-AG, thus increasing its availability [15]. The anxiolytic and antipsychotic effects of CBD were hypothesized to be mediated by CBD-induced accumulation of anandamide and 2-AG [16]. This is supported by research conducted on valproate-treated animal models of autism, where CBD was found to act as an inhibitor of the metabolic degradation of anandamide, which leads to the accumulation of the endocannabinoid, resulting in a reduction of social interaction deficits [10].

The evidence in this case study suggests CBD can alleviate many negative symptoms associated with autism with minimal patient side effects. Oral ingestion is the preferred route for drug delivery by patients and drug developers [17]. Successful drug delivery also depends on the individual’s physiology and the physicochemical properties of the drug, such as solubility, dissolution, stability, permeability, and metabolism. Since CBD is a highly lipophilic drug, when delivered orally in solution, it can precipitate in the gastrointestinal (GI) tract, resulting in an absorption rate slower than elimination [18]. Time to peak plasma concentration following oral delivery is slow for CBD (1-4 h), and the half-life of CBD was reported between 1.4 and 10.9 h after oromucosal spray [19]. One way to increase the oral bioavailability of CBD is to administer CBD with a high-fat and high-calorie meal, since the increased micelle formation allows the CBD to be more readily available for lymphatic transportation while inhibiting drug efflux transporter activities [17].

A study by Fletcher et al. reports the usage of extracts with a high CBD low THC ratio with average CBD doses ranging from 1.8 to 6.45 mg/kg/day, similar to the range used in this case study [18]. The routine starting dose recommended for the adult patient is 5mg of CBD-predominant cannabinoid twice daily [19]. CBD titration should include increasing the dose by 10 mg per day every two to three days until a maximum of 40mg/day is reached [19].

The patient and the caregiver in the case study did not report any side effects with treatment. In a clinical study with 33 children, restlessness was reported in 22% of the patients and decreased with dose adjustment [20]. In that same study, CBD was discontinued in a 13-year-old male patient with severe autism due to generalized seizures after using 5 mg sublingual CBD, and the seizures resolved after antiepileptic drug treatments [20]. There is limited pharmacology research on CBD, and the potential hazards of short and long-term use need to be further investigated. Consideration might be given for CBD use when caregivers choose to avoid traditional pharmaceuticals or failure of conservative therapy.

To improve the evidence on CBD efficacy in patients with ASD, a randomized, double-blind, and placebo-controlled clinical trial should be initiated to further research various strains of CBD-enriched cannabis extracts with different dosages and durations to investigate its safety, efficacy, and tolerability.

Conclusions

In this case, the child patient responded positively to the introduction of CBD oil treatment with reduced negative behaviors, better sleep, and improved communication. With the increasing clinical studies on the use of cannabidiol in treating patients with mood disorders, anxiety, chronic pain conditions, and other behavioral problems, it should be considered as a treatment option in managing symptoms related to autism. In the case study presented, the child patient has shown behavioral and cognitive improvements with no side effects reported. Altogether, this study presents a case that motivates further research and clinical studies to understand the molecular mechanism of CBD as well as the dosing regimes for pediatric populations, the etiology of ASD, and how various dosing affect different demographics.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Lucy Ma and Sofia Platnick contributed equally to the article and should be considered co-first authors.

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Trends
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Review Article

Cannabis and cannabinoid use in autism spectrum disorder: a systematic review

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Abstract

Introduction: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction, associated with the presence of restricted and repetitive patterns of behavior, interests, or activities. Cannabis has been used to alleviate symptoms associated with ASD.
Method: We carried out a systematic review of studies that investigated the clinical effects of cannabis and cannabinoid use on ASD, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA checklist). The search was carried out in four databases: MEDLINE/PubMed, Scientific Electronic Library Online (SciELO), Scopus, and Web of Science. No limits were established for language during the selection process. Nine studies were selected and analyzed.
Results: Some studies showed that cannabis products reduced the number and/or intensity of different symptoms, including hyperactivity, attacks of self-mutilation and anger, sleep problems, anxiety, restlessness, psychomotor agitation, irritability, aggressiveness perseverance, and depression. Moreover, they found an improvement in cognition, sensory sensitivity, attention, social interaction, and language. The most common adverse effects were sleep disorders, restlessness, nervousness and change in appetite.
Conclusion: Cannabis and cannabinoids may have promising effects in the treatment of symptoms related to ASD, and can be used as a therapeutic alternative in the relief of those symptoms. However, randomized, blind, placebo-controlled clinical trials are necessary to clarify findings on the effects of cannabis and its cannabinoids in individuals with ASD.
Systematic review registration: International Prospective Register of Systematic Reviews (PROSPERO), code 164161.
Keywords: Cannabis, cannabidiol, cannabinoid, autism, systematic review.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction, in multiple contexts, associated with the presence of restricted and repetitive patterns of behavior, interests, or activities.[1] In a multicenter epidemiological study performed in 2012, involving nine countries, the estimated average prevalence of ASD was 62 individuals per 10,000 inhabitants.[2] Children with autism commonly exhibit comorbidities such as hyperactivity, self-harm, aggression, restlessness, anxiety and sleep disorders.[3] This type of behavior favors social exclusion and limits the child's abilities, causing more distress to caregivers.[4]

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Conventional medical treatment includes several psychotropic drugs such as atypical antipsychotics, selective serotonin reuptake inhibitors, stimulants and anxiolytics; they do not treat ASD, but aim to eliminate inappropriate behavior, such as psychomotor agitation, aggressiveness, and obsessive-compulsive symptoms.[5-8] They may lead to severe side effects such as nephropathy, hepatopathy, and metabolic syndromes, among others.[9] Unfortunately, 40% of children with autism and disruptive behaviors do not respond well to standard medical and behavioral treatment.[4] This carries a high cost for the individual and society, causing life expectancy to be reduced by 20 years in patients with autism compared to the population average.[10]

Among the possible pharmacological treatments, researchers began to explore other therapeutic alternatives, such as the use of substances derived from *Cannabis sativa.*[11] Cannabidiol (CBD) represents one of the major components of the plant, having been studied in several disorders. At present, preliminary evidence suggests that CBD can relieve spasticity,[12] pain, sleep disorders,[13] improve mobility in multiple sclerosis,[14] in addition to relieving anxious symptoms and social phobia[15]; however, further studies are needed to prove its effectiveness.

In autism, cannabis and cannabinoids have also been used to treat symptomatic conditions.[16,17] CBD, and some other compounds in the plant, interact with the endocannabinoid system and can modulate different aspects related to cognition, socioemotional responses, susceptibility to seizures, nociception and neuronal plasticity, which are often altered in autism.[18-21] In mammals, the endocannabinoid system is mainly composed of two receptors, CB1 and CB2, endocannabinoids (endogenous substances that activate CB1 and CB2 receptors) and the enzymes responsible for their synthesis and metabolism.[22]

CB1 receptors are expressed in both the central and peripheral nervous systems, with their most abundant expression in basal ganglia nuclei and pre-synaptic GABAergic and glutamatergic neurons.[23] Considering that the endocannabinoid system modulates emotional responses, mood, behavioral reactions to the context and social interaction, investigators have started to formulate the hypothesis that changes in this system would be present in the autistic phenotype.[24] Aran et al.[25] observed reduced levels of endocannabinoids, such as anandamide (AEA), palmitoylethanolamide (PEA) and oleoethanolamine (OEA), in plasma samples from 93 children with ASD, suggesting the use of such substances as possible biomarkers for diagnosis. Pretzsch et al.[26] reported that CBD can change the levels of the metabolites Glx (glutamate + glutamine) and gamma-aminobutyric acid (GABA) – the metabolites that contribute to the regulation of excitatory and inhibitory neurotransmission, both in typical development and in ASD. In an uncontrolled single-case study, delta-9 tetra-hydrocannabinol (Δ9-THC) was administered to a 6-year-old autistic boy who was not taking any medication for 6 months. After the treatment period, there was a decrease in the scores of hyperactivity, lethargy, stereotyped behavior and language change, leading the authors to suggest the use of the substance as a resource to other treatments and early interventions.[27]

Thus, evidence has indicated that *Cannabis sativa* derivatives can alleviate symptoms associated with ASD, although there is still no consistent evidence about its efficacy, safety and tolerability, since no randomized, double-blind, placebo-controlled clinical trial with cannabis and cannabinoid for the treatment of the core symptoms of autism and coexisting symptoms have been conducted to date (only prospective studies are currently available). The research so far performed has shown that there are few side effects and, when they do occur, they are generally mild/moderate and transitory. In order to analyze such aspects, we carried out a systematic review of studies that used cannabis derivatives in autism, considering the evolution of symptoms and clinical improvement of these individuals.

Method

In October 2020, we carried out a systematic literature review following the rules of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) system. The study was registered in the International Prospective Register of Systematic Reviews database (PROSPERO) with the code 164161.

To support the review, the following questions were asked: 1) What is the efficacy, safety and tolerability of cannabis and cannabinoids in treating symptoms of ASD? 2) What are the main instruments used to assess the evolution of symptoms and clinical improvement?

The search was carried out in four databases: MEDLINE/PubMed, Scientific Electronic Library Online (SciELO), Scopus, and Web of Science. Additional studies were retrieved by checking the references of the selected articles. Finally, a search was performed using the Google Scholar tool. The search strategy for the databases was defined based on terms found in the title or abstract, using descriptors related to cannabis (cannabis, cannabidiol, cannabinoid, CBD, marijuana, marihuana, and hemp) and also descriptors related

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to autism (autistic, autism, Asperger, and pervasive development disorder). During the selection process, no restrictions were applied in terms of language, e,g., any article found was included in the eligibility analysis. Descriptors were included in quotation marks, and the search operators "AND" and "OR" were used. Cannabis-related terms were grouped using the "OR" operator; terms related to autism were grouped similarly. Then, these two groups of related terms were added and joined by the "AND" operator (Figure 1).

We included all articles published until October 2020, in any language, in the form of clinical trials or case studies involving human beings. Articles unrelated to the topic, i.e., those reporting on illicit or recreational use of cannabis, as well as abstracts, book chapters, animal studies, and research on other pathologies or changes that were associated with signs and symptoms similar to those observed in autism, were rejected.

The articles found in the databases were initially screened by reading their titles and abstracts. Subsequently, those articles considered to meet the proposed topic were read in full. At the end of the screening phase, we browsed the references of the articles ultimately selected in search of other studies that met the eligibility criteria.

The search and screening of the selected articles were carried out simultaneously and independently by two authors. In the end, the disagreements found were sent to another author, to make the final decision about whether or not to include a certain study, but always checking the eligibility criteria.

The searches conducted in the MEDLINE/PubMed, SciELO, Scopus, and Web of Science databases yielded 64, 1, 242, and 125 articles, respectively. Of these, respectively, 58, 1, 237, and 121 articles were eliminated because they did not meet the inclusion criteria. Thus, 14 studies were found, which, after eliminating duplicates, resulted in six articles. From the browsing of references of these six studies, another paper was selected to be part of the review, making a total of seven selected articles. Finally, the search carried out on Google Scholar yielded two more studies, reaching a final total of nine articles included in this systematic review, in accordance with the inclusion and exclusion criteria adopted (Figure 1).

The data extraction method of each study consisted in filling a standardized information sheet. One reviewer extracted the scientific data, and a second reviewer verified the acquired information. Disagreements were resolved by discussion and consensus among the authors-reviewers.

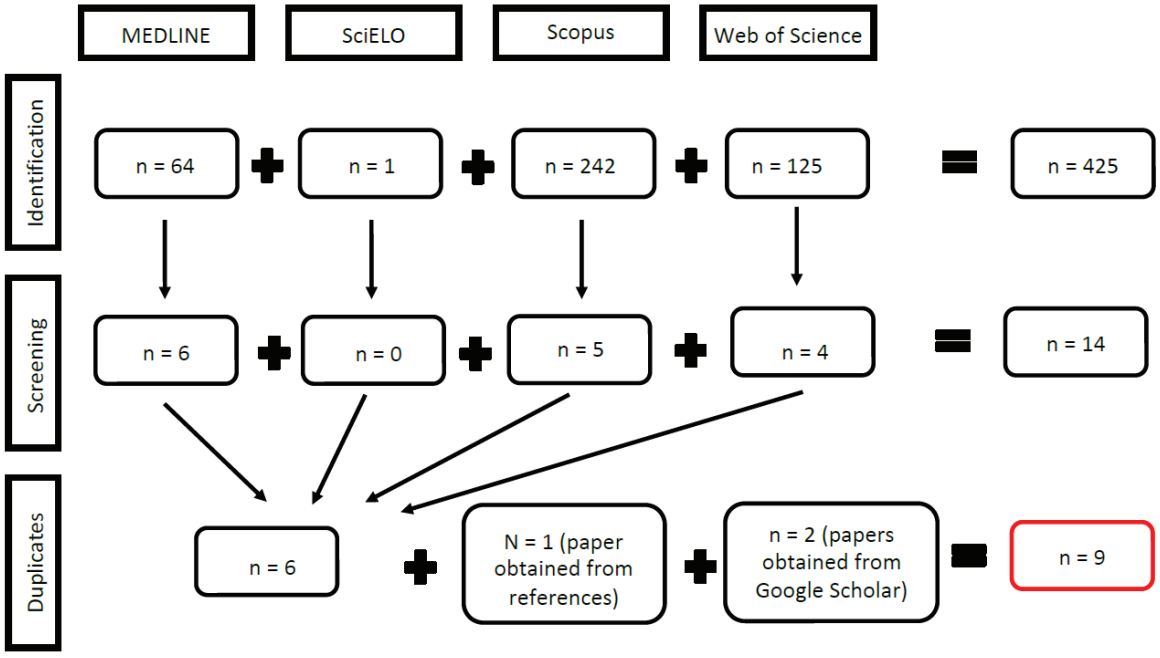

Figure 1 - Study selection flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for cannabis and cannabinoid use in autism spectrum disorder.

Results

The initial results of the search returned 425 articles. After the first screening, 411 were excluded for not meeting the inclusion or exclusion criteria, due to the following reasons: primary research on the endocannabinoid system or on other mental disorders (172), book chapters, conferences or editorials (87), research on animals (26), review articles (85), research investigating the effects of illicit or recreative use of cannabis (35), studies on other disorders and conditions that overlap with some symptoms of ASD (6). Afterwards, eight articles were found to be duplicates and were therefore excluded, resulting in six articles retrieved from MEDLINE/PubMed, Scopus, and Web of Science. Finally, there was the addition of two studies found in Google Scholar and one article found through the analysis of references of the previously selected articles, at a final total of nine articles for analysis (Table 1).

The countries of origin of the studies included in the systematic review were: Israel (three studies), England (three studies), Brazil (one study), Austria (one study), and the United States (one study).

Five studies used cannabis extract, in the presentation of CBD-rich oil,[16,17,28,30,31] two studies used CBD in oral solution,[26,28] one study used dronabinol, which is a synthetic analogue of THC (tetrahydrocannabinol), dissolved in sesame oil,[27] and one study used cannabidivarin (CBDV)[32] (Table 1).

The studies using CBD-enriched cannabis oil showed a variation between the proportions of CBD and THC, ranging from 6 to 75% CBD combined with 1 to 1.5% THC. Those who used pure CBD used a dose of 600 mg (oral solution), dronabinol was used at a dose ranging between of 0.62 and 3.62 mg/day (dissolved in sesame oil), and cannabidivarin was used at a dose of 600 mg.

The samples were composed of: 1) children in three studies[16,17,27]; 2) children and adolescents in one study, with ages ranging from 5 to 19 years[29]; and 3) adults in three studies.[26,28,32] Two studies did not specify the age group.[30,31]

Only three studies used any imaging exam, namely, magnetic resonance spectroscopic imaging after the intervention with CBD in two studies and with CBDV in one study to search for brain changes.[26,28,32] The other studies used questionnaires, forms and subjective reports of family members or caregivers. Of the nine

Table 1 - Studies selected for systematic review of the use of cannabis and cannabinoids for ASD

Title, authors and year	Country	Sample	Method	Results	Conclusion
Brief report: Cannabidiol rich cannabis in children with autism spectrum disorder and severe behavioral problems--a retrospective feasibility study Aran et al., 2018[17]	Israel	60 children (mean 11.8 years old, SD 3.5 years), 83% male, 77% with low cognitive function (according to ADOS or CARS), all with severe behavior problems (6 or 7, according to CGI-S).	Retrospective analysis of autistic children with behavioral changes refractory to conventional treatment at the Shaare Zedek Medical Center (Jerusalem, Israel), with medical prescription of cannabis for 7 to 13 months with plant extract containing CBD and THC at 20:1 (in poorly responsive cases, 6:1).	The average daily dose was 3.8±2.6 mg/kg/day of CBD and 0.29±0.22 mg/kg/day of THC for the 44 children who received three doses/day. For the 16 who received two doses, 1.8±1.6 mg/kg/day of CBD and 0.22±0.14 mg/kg/day of THC was the average dose received. 51% presented one side effect, the most common being: sleep disorders (14%), restlessness (9%), nervousness (9%), and loss of appetite (9%). In the HSQ score, 29% had an average improvement of 1.38±1.79 (median = 0.81). In the APSI score, it was 0.66±0.74 (median = 0.53).	There was a significant improvement in behavioral problems that was reported in 61% of children, in the CGIC; in anxiety: 39% and in communication problems: 47%. High concentration of THC (6:1-CBD) can lead to a psychotic episode.
Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and comorbidities Barchel et al., 2018[16]	Israel	53 children (mean 11 years of age, SD 4 to 22 years) received CBD for an average of 66 days (SD 30-588 days).	Administration of oil with CBD and THC (20:1), orally, with telephone interviews conducted every two weeks with parents or caregivers, asking about changes in symptoms, the data obtained were analyzed independently by specialists in search of these changes in symptoms and safety of medicines. The improvement resulting from CBD was also compared with conventional treatment for ASD.	Self-harm and anger bouts (n = 34) improved in 67.6% and worsened in 8.8% of the participants. Symptoms of hyperactivity (n = 38) improved in 68.4%, did not change in 28.9%, and worsened in 2.6% of the subjects. Sleep problems (n = 21) improved in 71.4% and worsened in 4.7%. Anxiety (n = 17) improved in 47.1% and worsened in 23.5% of the participants. Adverse effects, mostly somnolence and change in appetite, were mild.	A comparison of symptom improvement between CBD treatment and conventional treatment was analyzed using the binomial test. Parents' reports suggest that CBD may improve symptoms related to ASD.

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Table 1 (cont.)

Title, authors and year	Country	Sample	Method	Results	Conclusion
Effects of cannabidiol on brain excitation and inhibition systems: a randomized placebo-controlled single dose trial during magnetic resonance spectroscopy in adults with and without autism spectrum disorder Pretzsch et al., 2019[26]	England	34 people (neurotypical control n = 17, ASD n = 17). All with IQ greater than 70.	Patients were allocated in a randomized order: about half in each group participated in the placebo before CBD (600 mg oral solution) and the other half participated in CBD before the placebo. After administration, placebo or CBD, a check was scheduled to coincide with the maximum plasma concentration (2 h). It was evaluated by magnetic resonance spectroscopic imaging.	It was seen that patients with ASD had a drop in IQ compared to neurotypical controls (F_1 = 5,781; p = 0.022), but the difference in IQ did not influence the results: ASD (r < -0.008; p > 0.698); neurotypical (r < 0.068; p > 0.235). The excitatory mechanisms of response to glutamate were comparable, regardless of diagnosis, however the inhibitory response by GABA + was altered in ASD. There was a difference in the results found in the images in relation to the placebo group.	CBD can change the levels of glutamate, glutamine and GABA +, regulators of excitatory and inhibitory neurotransmission. The autistic brain reacts differently to GABA+, which helps to understand the mechanisms and targets of treatment for ASD.
The effect of cannabidiol (CBD) on low-frequency activity and functional connectivity in the brain of adults with and without autism spectrum disorder (ASD) Pretzsch et al., 2019[28]	England	34 people (17 with ASD and 17 without).	CBD 600 mg oral solution. Functional magnetic resonance imaging was used for evaluation.	CBD is able to alter the fALFF in the cerebellar vermis, center of perception of gravity, right fusiform gyrus. The connectivity function (FC) in the vermis increased in the left and right caudal portion, however it reduced between the vermis and the occipital temporal part of the left middle temporal gyrus, the right supramarginal anterior gyrus, the left upper parietal lobe and the gyrus upper left front; none of these effects were observed significantly in the brains of healthy people. There was a difference in the results found in the images in relation to the placebo group.	First evidence of neuromodulation made from the administration of CBD in fALFF and FC in the brains of adults with autism. CBD was able to alter crucial properties of brain function in key areas that are altered in ASD.
Real life experience of medical cannabis treatment in autism: analysis of safety and efficacy Bar-Lev Schleider et al., 2019[29]	Israel	188 patients with ASD with a mean age of 12 years, SD ± 7 years, younger than 5 years (14). 81.9% of the male gender.	Cannabis oil enriched with 30% CBD and 1.5% THC (3 times a day, sublingual) was used, oil enriched by an average of 61.5 + -79.5 mg CBD and 3 + -4 mg THC. The team initially and periodically evaluated the health status, assessed the medical history and administered medical questionnaires.	In 6 months (49.5% of sample loss), 91% of cases of restlessness improved; 90.3% of anger bouts; 85.2% of agitation; 78.1% problems with sleep; among other symptoms. There was at least one side effect in 25.2%, which were: restlessness (6.6%), drowsiness (3.2%), psychoactive effect (3.2%), increased appetite (3.2%), digestive problems (3.2%), dry mouth (2.2%) and lack of appetite (2.2%).	The use of cannabis for ASD is well tolerated, safe and appears to be effective in relieving symptoms (especially seizures, depression, restlessness and bouts of anger). There was great acceptability of the treatment, with only less than 15% of dropouts in a 6-month follow-up. More than 80% of parents reported a significant global improvement in children.
Use of dronabinol (delta-9-THC) in autism: A prospective single-case-study with an early infantile autistic child Kurz & Blaas, 2010[27]	Austria	Boy, 6 years old, (diagnosed at 3) via DSM-IV criteria and confirmed by ADOS and ADI.	Drops of dronabinol dissolved in sesame oil, with one drop initially (0.62 mg) in the morning up to the maximum dose of 2 drops in the morning, with a total daily dose of 3.62 mg of dronabinol. 6-month follow-up (without adding other new therapies or changing existing care measures). Symptom severity was assessed using the ABC questionnaire.	Hyperactivity decreased by 27 points, lethargy reduced by 25 points, irritability decreased by 12 points, stereotypy reduced by 7 points and inappropriate speech decreased by 6 points in six months.	This isolated case suggests that dronabinol may reduce the symptoms of autism in children, perhaps by modifying cannabinoid levels in the central nervous system.
Rating of the safety and effectiveness of marijuana, THC/CBD, and CBD for autism spectrum disorders: results of two national surveys Adams et al., 2019[30]	United States	156 participants who already used cannabis in its derived forms.	The National Survey on Treatment Effectiveness for Autism (NSTEA) started collecting data in 2017 and continues to collect online. Marijuana is studied in the following forms: flower, edible, vaporized, gums, tincture, leaf and other forms; THC/CBD combination in the following forms: oil, gums, edible, tincture, vaporized and all methods; and only CBD in the following forms: oil, tincture, gums and others.	Reported improvements: calm (58-71%); irritability (46-65%); aggression/agitation (43-58%); sleep (30-58%); drowsiness (32-46%); hyperactivity (26-39%); sensory sensitivity (28-32%); cognition (32-46%); attention (26-42%); social interaction (26-42%); language (26-38%); perseverance (22-27%); depression (16-41%). Adverse effects of CBD, uncommon: behavioral problems (5%), decreased cognition (4%), fatigue (4%), aggression/agitation (4%). All these side effects were mild and/or transient.	The primary reported benefits were calming effects, including improved anxiety, irritability, aggression/agitation, hyperactivity, and sleep. There were also improvements in the symptoms of ASD. There were few adverse effects for THC/CBD and CBD and mild for marijuana.

Continued on next page

Table 1 (cont.)

Title, authors and year	Country	Sample	Method	Results	Conclusion
Effects of CBD-enriched *Cannabis sativa* extract on autism spectrum disorder symptoms: an observational study of 18 participants undergoing compassionate use Fleury-Teixeira et al., 2019[31]	Brazil	18 patients: 11 without a history of epilepsy, 2 with a previous history of epilepsy but without seizures for over a year, and 5 with epilepsy and still with seizures.	Extract enriched with CBD in the ratio CBD/THC 75:1. Average of 4.6 mg/kg/day of CBD and 0.06 mg/kg/day of THC. The individual doses were based on previous studies with patients with refractory epilepsy associated with autism. The average initial dose was 2.9 mg/kg/day and dose adjustments were made throughout the treatment.	80% of patients improved in more than 30% of the three items assessed: sleep disorders, epileptic seizures, and behavioral changes. In addition, signs of improvement were reported for motor development; communication and interaction; and cognitive performance. The adverse effects were: moderate drowsiness and irritability (three cases each), diarrhea, increased appetite, conjunctival hyperemia, and increased body temperature (one case each). All these side effects were mild and/or transient.	Several therapeutic benefits of the CBD-enriched preparation that extends to ASD symptoms have been noted, even in non-epileptic patients. This study pointed to a potential risk of paradoxical effects when introducing cannabinoids to a patient using a combination of drugs that include antipsychotics. This highlights the need for extra vigilance and a gradual increase in the dosage of cannabinoids in patients receiving many medications.
Effects of cannabidivarin (CBDV) on brain excitation and inhibition systems in adults with and without autism spectrum disorder (ASD): a single dose trial during magnetic resonance spectroscopy Pretzsch et al., 2019[32]	England	34 participants, around 28.47 (6.55) years old in the control group and 31.29 (9.94) in those with ASD, among them 17 people, diagnosed by ICD-10, with severe symptoms evaluated by ADOS and ADI.	Randomized, double-blind, crossover study using magnetic resonance spectroscopic imaging comparing glutamate and GABA levels after the use of placebo and 600 mg CBDV. Information was collected from the dorsomedial region of the prefrontal cortex and the left basal ganglia (areas related to ASD) after 2 h (plasma peak of the substance) of administration.	Tests performed at least 13 days after using the drug/placebo indicated that CBDV increased the levels of glutamate in the left basal ganglia in both groups, but in those with ASD despite this increase, the basal concentration of the substance decreased. CBDV did not alter the levels of glutamate or GABA in the medial dorsal region of the prefrontal cortex of either group. There was a difference in the results found in the images in relation to the placebo group.	CBDV modulates the levels of glutamine/GABA in the left basal ganglia, with individual variations depending on the biochemistry of the individual base (CBDV increased the levels of glutamate in autistic low baseline amounts, opposite to those who already had it high in baseline). Future studies should evaluate the effect of CBDV on behavior and whether the response to an acute dose can predict therapeutic success in patients with ASD.

ABC = Aberrant Behavior Checklist; ADI = Autism Diagnostic Interview; ADOS = Autism Diagnostic Observation Schedule; APSI = Autism Parenting Stress Index; ASD = autism spectrum disorder; CARS = Childhood Autism Rating Scale; CBD = cannabidiol; CBDV = cannabidivarin; CGIC = Caregiver Global Impression of Change; CGI-S = Clinical Global Impression Scale – Severity; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; fALFF = fractional amplitude of low-frequency fluctuations; FC = connectivity function; GABA = gamma-aminobutyric acid; HSQ = Home Situations Questionnaire; ICD-10 = International Classification of Diseases, 10th revision; IQ = intelligence quotient; SD = standard deviation; TBI = craniocerebral trauma; THC = tetrahydrocannabinol.

studies selected for the systematic review, with the age groups already described above, one had placebo allocated to participants in a randomized order, with half of the sample using CBD before vs. half after using the placebo[26]; two were randomized, double-blind and placebo-controlled[28,32]; in the remaining studies, the intervention of cannabis or cannabinoids was administered without randomization, as previously described. It is important to note that none of the studies evaluated included the cognitive assessment of children through neuropsychological tests.

Regarding the results found, the studies that tested cannabis to improve behavior showed improvement in many individuals with ASD. The following symptoms were targeted: bouts of self-mutilation and anger, hyperactivity, sleep problems, anxiety, restlessness, psychomotor agitation, irritability, aggressiveness, sensory sensitivity, cognition, attention, social interaction and language change, perseverance, and depression (Table 1).

Of the studies evaluated, a small percentage of individuals, about 2.2 to 14%, presented side effects with the use of cannabis products, such as sleep disorders, restlessness, nervousness and change in appetite, in addition to moderate irritability, diarrhea, increased appetite, conjunctival hyperemia, behavioral problems, decreased cognition, fatigue and aggression/agitation.[16,17] There was a psychotic symptom in one child, in a single-case study[17]; she interrupted treatment with CBD and THC and switched to ziprasidone 1.4 mg/kg/day. The symptoms resolved after 9 days.

Discussion

Autism is part of a group of serious neurodevelopmental diseases that begin early in life and for which no specific treatment is available so far. ASDs are characterized by altered social interaction, compromised verbal and nonverbal communication,

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stereotyped and repetitive behaviors,[1] often associated with social comorbidities[3,33,34] and generalized anxiety.[35-37]

This systematic review sought to investigate whether cannabis-based products could bring any benefit to patients with ASD. From the nine studies evaluated, it was possible to observe that the cannabis products used were able to improve some symptoms related to ASD, e.g., self-mutilation and anger bouts, hyperactivity, sleep problems, anxiety, psychomotor agitation, irritability, aggressiveness, sensory sensitivity, cognition, attention, social interaction, language change, depression, and especially restlessness.

Cannabis sativa has over 500 identified active chemical constituents, and about 100 of them are classified as phytocannabinoids. The main phytocannabinoid is THC, responsible for the psychoactive effects of the plant, followed by CDB, exempt from this activity.[38-40]

The promising results found in this systematic review may be associated with the action of the phytocannabinoids present in the plant on the regulation of the endocannabinoid system. The endocannabinoid system is a unique biological system that affects a wide range of biological processes, including brain development and functioning. It consists of cannabinoid receptors (CB1 and CB2, mainly expressed in the brain and periphery, respectively), their endogenous ligands (endocannabinoids, mainly AEA and 2-arachidonoylglycerol [2-AG]), and enzymes for ligand synthesis and degradation.[19-22] Endocannabinoids are key modulators of socioemotional responses, cognition, seizure susceptibility, nociception and neuronal plasticity,[23-26] all of which are affected in ASD.

Endocannabinoids are known to regulate the main brain functions that are altered in ASDs.[41] A well validated animal model of ASD based on prenatal exposure to valproic acid in rats has been used to evaluate behavioral alterations.[42,43] There is strong evidence suggesting that altered levels of AEA, which already manifest in childhood and persist in adolescence and adulthood, may be associated with autistic symptoms, thus providing preclinical justification for a potential role of AEA signaling as a new therapeutic target for ASD. These results have corroborated a series of preclinical data that suggest that AEA signaling seems to play a modulating role on rodent behaviors associated with symptoms of ASD.[21] A pioneering clinical study was able to identify low levels of AEA in plasma from children with ASD compared to plasma from children without ASD. These preliminary results corroborate the preclinical evidence that signs of AEA may be impaired in patients with ASD.[44]

A study conducted in 2019 by Aran et al.[25] showed strong evidence that serum levels of certain endocannabinoids, mainly AEA and its structurally related compounds, are substantially reduced in people with ASD, regardless of age group or gender. That study has several limitations: uncontrolled retrospective study of a subgroup of children with severe and refractory behavioral problems; participants used several cannabis strains from different growers and a wide range of doses of CBD and THC; and the number of participants was not large enough to assess the impact of treatment on different subgroups of ASD.

It is important to note that endocannabinoids are not stored in any cell compartment for later use. They are generated on demand from the post-synaptic neuron cell membrane and are rapidly inactivated by pre-synaptic cell uptake and enzymatic hydrolysis. As a result, the concentrations of the various endocannabinoid pathways in the brain are constantly regulated, and even small changes in these concentrations can be clinically significant.[25]

Most of the studies evaluated in this systematic review used cannabis oil with higher CBD content when compared to the other phytocannabinoids present in the oil, at different proportions. Some studies have shown that CBD is capable of inhibiting the fatty acid amide hydrolase (FAAH), an enzyme responsible for the degradation of AEA, increasing its levels in the synaptic cleft[45,46]; this increase may be associated with an improvement in some ASD symptoms after use of CBD-rich cannabis products.

In a single-case study, Kurz & Blaas[27] demonstrated that dronabinol, a synthetic analogue of THC, in doses ranging from 0.62 to 3.62 mg/day, was able to improve symptoms of hyperactivity, aggression, stereotyped and inappropriate speech. Notwithstanding, pure THC has not been commonly used, because the substance is responsible for most of the psychoactive effects of the plant.[47] Crippa et al.[48] report that CBD is capable of preventing the induction of psychotic symptoms induced by THC, suggesting that both substances could be useful used in combination.

Sometimes, patients with ASD need to make use of typical and atypical antipsychotics, anticonvulsants and mood stabilizers to control behavioral-mental changes such as psychomotor agitation and self- and/or heteroaggressiveness; psychostimulants and the antihypertensive clonidine to improve concentration and/or hyperactivity; serotonin inhibitors to improve obsessive-compulsive symptoms, anxiety disorders, depression and stereotypes. However, these drugs can cause serious side effects, such as nephropathy, hepatopathy, and metabolic syndrome, among others.[9]

In this systematic review, the cannabis products used in patients with ASD showed mild and moderate

side effects, such as sleep disturbances, restlessness, moderate irritability, diarrhea, increased appetite, conjunctival hyperemia, behavioral problems, decreased cognition, fatigue, and aggression/agitation[16,17] – effects not as severe as those observed with classic drugs.

In one of the studies included in this review, Adams et al.[30] investigated the effectiveness of marijuana in a variety of diseases, including autism. Participants in this study used the plant, containing both CBD and THC, in different forms: flower, edible, vaporized, chewing gum, dye, leaf, oil, as well as isolated CBD. They observed improvements in some symptoms associated with ASD, e.g., anxiety, irritability, aggression, hyperactivity, and sleep, with mild adverse effects. Therefore, it is possible to observe that cannabis products appear to be safer when compared to the drugs traditionally used in the treatment of ASD-related symptoms.

Of the articles evaluated, only the three double-blind, placebo-controlled clinical trials that used CBD or CBDV alone assessed the influence of the substance on the central nervous system through functional magnetic resonance imaging (fMRI).[26,28,32] Moreover, there was a difference in the results found in the images in relation to the placebo group, but the evolution of clinical symptoms or side effects could not be evaluated, as individuals used cannabis only once.

fMRI pattern after using CBD

A 600 mg CBD oral solution was used in individuals with ASD who underwent fMRI to assess the effects of this treatment on their central nervous system.[26,28,32] All those studies were carried out by the same team of researchers; 17 neurotypical adults and 17 adults with autism were administered a 600 mg CBD oral solution at one occasion, and a placebo substance at another occasion (randomized order); patients were then examined using fMRI. CBDV increased the levels of glutamate in the left basal ganglia, assessed with spectroscopy; however, in patients with ASD, despite the increase, the basal concentration of the substance decreased.[32]

It was noticed that CBD and CBDV altered the GABAergic system in all participants. The excitatory mechanisms of response to glutamate did not differ between the two groups, however the inhibitory response mediated by GABA was different in people with ASD, indicating that the brain of an autistic individual has a distinct GABAergic system from that of neurotypical individuals. In other words, the autistic brain reacts differently to GABA, and this discovery may help understand the mechanisms and targets of treatment in autism. Pretzsch et al.[28] were pioneers for publishing the first evidence of neuromodulation made from the administration of CBD in fractional amplitude of low-frequency fluctuations and connectivity function in the brains of adults with ASD.

This finding is consistent with previous studies that pointed out differences in the functioning of the GABAergic system of people with autism and typical individuals, without the use of any substance.[49] In addition, CBD was able to change the fractional low-frequency oscillation amplitude and functional connectivity in the adult brain in key regions commonly associated with the ASD condition. The authors of all studies did not mention any data about side effects or cognitive and/or behavioral changes. Also, it must be considered that the effects of a single administration were observed, and it is therefore not possible to predict long-term results of use.[28]

For Gallily et al.,[50] the ideal form would be the use of the CBD-enriched extract; according to the authors, the use of isolated CBD brings a bell-shaped dose-response relationship, which would limit its clinical use. Conversely, the extract brought an increasing result after increasing the dose, improving anti-inflammatory and anti-nociceptive responses in mice.

Clinical results of using cannabis to treat ASD symptoms without magnetic resonance imaging

The six articles that observed the effect of cannabis on the clinical aspects of children, adolescents and adults with ASD showed improvements in several behavioral aspects, regardless of the substance or composition employed. However, comparing the magnitude of the results is not possible, as the authors used different designs to measure and present the results – what they do have in common is the suggestion that cannabis could be a therapeutic alternative to autism. In all six articles evaluated, it was possible to observe an improvement in the following symptoms associated with autism: decreased bouts of self-mutilation and anger, hyperactivity, sleep problems, anxiety, restlessness, psychomotor agitation, irritability, perseverance, aggressiveness, and depression. Improvement in sensory sensitivity, cognition, attention, social interaction, and language were also reported. These results confirm the prediction of Khalil,[51] who mentioned the need for systematic investigations into ASD and cannabis. That author argued that the tranquilizing, sedative and anticonvulsant properties of cannabis could assist in the main difficulties faced by children with autism, recognizing the behavioral and cognitive evolutions of cannabis in other pathologies and making a bridge with the mentioned results.

Most of the studies evaluated in this systematic review measured the evolution of symptoms through

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the perception of improvement by parents/caregivers of symptoms secondary to ASD, using questionnaires or scales developed by the authors themselves. None of the articles mentioned the use of neuropsychological assessments to investigate cognitive aspects.

Fleury-Teixeira et al.[31] warned about the need for extra vigilance and a gradual increase in the dose of cannabinoids in patients using other psychotropic drugs. In those authors' study, the symptoms of drowsiness, irritability, diarrhea, increased appetite, conjunctival hyperemia, and increased body temperature were seen in some cases and considered mild and/or transient. Few participants had to interrupt treatment before the end of the first month, due to adverse effects such as insomnia, irritability, rapid heartbeat, and worsening of the psychobehavioral crisis. The patients who had relevant side effects were all taking several medications, including at least one antipsychotic. A possible bias could be that the presence of epilepsy (38.9% of participants) may have interfered with the outcome, as studies that report improvement in epilepsy often also describe ASD-related symptoms.

It is important to highlight that all the randomized double-blind studies found on the use of cannabis and cannabinoids for autism assessed brain structures through magnetic resonance imaging, but did not have a focus on the efficacy and safety of cannabis for ASD. All evaluations were observational, either in individuals who started the medication in the study and were observed prospectively, or in those who had already used the substance and were analyzed retrospectively.

As general limitations of the studies included in this systematic review, it possible to cite the absence of follow-up evaluations and the lack of laboratory tests to help confirm the safety of the substances used. Also, only six studies evaluated the patients clinically; the others were based on image examination only. Samples were small, and several participants were lost along the study period. Finally, endocannabinoids were not dosed.

Conclusion

Cannabis and cannabinoids have very promising effects in the treatment of autistic symptoms and can be used in the future as an important therapeutic alternative to relieve those symptoms, especially bouts of self-mutilation and anger, hyperactivity, sleep problems, anxiety, restlessness, psychomotor agitation, irritability, and aggressiveness; as well as improve sensory sensitivity, cognition, attention, social interaction, language, perseverance, and depression.

In addition, it is important to note that CBD can also change the levels of glutamate, glutamine and GABA, substances that contribute to the regulation of excitatory and inhibitory neurotransmission in both neurotypical and autistic individuals. However, randomized, double-blind and placebo-controlled clinical trials, as well as longitudinal studies, are necessary to clarify the findings on the effects of cannabis and its cannabinoids in individuals with autism.

Cannabis has been prescribed on an individual basis only, with autism being the second largest disease with available use, surpassed only by epilepsy. Therefore, it is essential to analyze what we have so far in the scientific literature, as cannabis is already being used worldwide as a phytopharmaceutical or as a CBD-rich cannabis extract for the autism spectrum.

Disclosure

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Safety and Efficacy of Medical Cannabis in Autism Spectrum Disorder Compared with Commonly Used Medications

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Abstract

Objective: The objective of this study was to evaluate the safety and efficacy of medications commonly used in autism spectrum disorder (ASD) and compare this to what current research has shown regarding medical cannabis use in this population.

Methods: Searches were performed to collect information surrounding currently used medications and their safety and efficacy profiles, biologic plausibility of cannabis use for symptoms of ASD, and studies detailing cannabis' safety and efficacy profile for use in the ASD population. Results were used to compare medications to cannabis as a proposed treatment.

Results: The heterogeneity of ASD produces great difficulties in finding appropriate treatment, leading to many medication changes or treatment trials throughout a patient's life. Commonly prescribed medications display varying levels of efficacy, safety, and tolerability between patients and symptoms targeted. Some of the most common side effects cited are also considered the most troubling symptoms associated with ASD; aggression, anxiety, irritability, and a negative effect on cognition, leading many patients to discontinue use as the side effects outweigh benefits. Recent case reports and retrospective studies have displayed the potential efficacy, safety, and tolerability of cannabidiol (CBD)-rich medical cannabis use for treating both core symptoms of ASD and many comorbid symptoms such as irritability and sleep problems. Studies have also identified circulating endocannabinoids as a possible biomarker for ASD, providing another possible method of diagnosis.

Conclusions: Currently, there are no approved medications for the core symptoms of ASD and only two medications Food and Drug Administration approved for associated irritability. Prescribed medications for symptoms associated with ASD display varying levels of efficacy, safety, and tolerability among the heterogeneous ASD population. At the time of this study there are no published placebo-controlled trials of medical cannabis for ASD and the observational studies have limitations. CBD-rich medical cannabis seems to be an effective, tolerable, and relatively safe option for many symptoms associated with ASD, however, the long-term safety is unknown at this time.

Keywords: cannabinol; medical marijuana; pharmaceuticals; tetrahydrocannabinol; psychopharmacology; autism spectrum disorder

Introduction

Autism spectrum disorder (ASD), as defined by the Centers for Disease Control and Prevention (CDC), is a developmental disability that can cause significant social, communication, and behavioral challenges. Diagnostic criteria for ASD from *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-V) are as follows[1]:

- Persistent deficits in social communication and social interaction across multiple contexts, manifested by deficits in social/emotional reciprocity, nonverbal communicative behaviors, or in developing, maintaining, and understanding relationships.
- Restricted, repetitive patterns of behavior, interests, or activities, manifested by stereotyped or

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repetitive motor movements, insistence on sameness, inflexible adherence to routines, or ritualized patterns of behavior, highly restricted, fixated interests that are abnormal in intensity or focus, or hyper- or hyporeactivity to sensory input.
- Symptoms must be present in early developmental period.
- Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
- Disturbances are not better explained by intellectual disability or global developmental delay.

While not in the diagnostic criteria, irritability, and aggression are some of the most common and challenging symptoms. In addition to these diagnostic criteria, symptoms vary greatly between patients, ranging from minimal to profound challenges that impact daily living.[2] In addition to the symptoms listed above, most patients with ASD also suffer from comorbidities, such as attention-deficit/hyperactivity disorder (ADHD), intellectual disability, epilepsy, sleep disorders, anxiety, and many other psychiatric or medical comorbidities.[1,2] These comorbidities and the heterogeneity of ASD symptoms make it difficult to appropriately treat the disorder, leading to many medication changes or treatment trials throughout the patient's life.[3]

Current interventions focus on behavioral and educational therapies, with pharmacotherapy playing a minor role.[4] Pharmacotherapy is primarily used to address symptoms, such as irritability, aggression, hyperactivity, tantrums, rapidly changing mood, and deliberate self-injury, which lead to greater difficulties in social communication and interaction.[5]

Risperidone and aripiprazole are approved by the U.S. Food and Drug Administration (FDA) to address irritability associated with ASD.[6] Currently, no other drugs are FDA approved for use with ASD. However, many medications, such as selective serotonin reuptake inhibitors (SSRIs) and stimulants, are used off-label to address the troubling symptoms of ASD.[7] A study by Madden et al.[8] found that close to half of insured children with ASD are receiving pharmacologic interventions with stimulants, antipsychotics, and antidepressants.

In addition, many parents are seeking help through alternative methods, such as natural remedies, supplements, and chelating agents.[9] Similarly, ASD support groups and parents are looking at cannabis as a potential treatment for symptoms associated with ASD.[10] In 2019, the state of Colorado passed House Bill 19-1028, which added ASD to the list of qualifying conditions for medical cannabis and encouraged further research exploring medical cannabis as treatment of pediatric conditions, including ASD.[11]

Due in part by the rising evidence of biologic plausibility for cannabis as a possible treatment for ASD patients and the ever-increasing number of states legalizing medical cannabis use, parents and providers alike are looking at cannabis as a possible solution to the current gap in treatment options for ASD.[12,13] This review aims to evaluate the safety and efficacy of cannabis as a potential treatment for ASD and comparatively evaluate commonly used medications based on their safety and efficacy profiles in this population.

Methods

A review of current literature on the treatment of ASD symptoms with both pharmaceuticals and cannabis was conducted through Google Scholar and Medline. Any articles that included research regarding medications for ASD, the biologic plausibility surrounding cannabis and ASD, and information on the safety and efficacy of cannabis use in this population were considered. A symptom-specific approach was used in this review.

An initial search was performed to determine the amount of research currently available regarding therapeutics and cannabis for ASD. Phrases used for this search included; "Autism Spectrum Disorder," "autism," "medication," "cannabis," "marijuana," "cannabinoids," "marihuana," "hash oil," "hashish," and medical subject heading (MeSH) terms for "autistic disorder," "cannabis," "cannabinoids," "therapeutics," "marijuana smoking," and "marijuana abuse." Relevant studies cited in other articles were also included in reviews.

Subsequent searches regarding medications used for ASD were narrowed to include specific drug names for the most commonly used pharmaceuticals. Preference was given to recent randomized controlled trials (RCTs) testing the safety and efficacy of the medication for use in the ASD population, specifically children and adolescents with ASD.

Due to the paucity of research regarding cannabis use as a potential treatment for ASD, narrowing of search criteria was not necessary for this section. Animal studies and opinion articles were excluded to maintain an unbiased and relevant up-to-date review of cannabis safety and efficacy for use in the human ASD population.

Research providing insight into the biologic plausibility of cannabis use for ASD was found by searching "autism spectrum disorder" and "cannabinoids" or "cannabis" and by scanning the references of included articles about cannabis safety and efficacy for use in the ASD population. Many of these articles are based on information found through animal studies investigating the endocannabinoid system, and thus were included based on applicability of information presented.

All publications were reviewed in detail to assess the population included in the study, exposures and outcomes measured, any potential biases or limitations, and the quality of evidence provided. Quality of evidence was determined based on GRADE principles.[14] Additionally, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was referenced while conducting this review to provide a basis in constructing this report.[15]

Medications Commonly Used for ASD

Due to the diverse nature of ASD, various medications have been investigated for their effectiveness in treating ASD symptoms. Currently used medications typically target specific troubling symptoms, with irritability receiving the most coverage.[6]

As part of a national survey on treatment effectiveness for autism by Coleman et al.,[7] 505 participants rated the benefits and adverse events on 26 commonly prescribed medications. This study provides valuable information about which symptoms of ASD experience benefit from different medications and the side effect profile of those medications, allowing determination of overall effectiveness.

Due to the heterogeneity of ASD, many patients try several different medications before finding one that provides the desired relief. The survey by Coleman et al.,[7] found that 11% of children (0–12 years) with ASD had tried four or more medications and 18% of teens (13–18) had tried six or more medications. In addition, many patients experience symptom severity that cannot be managed by one medication alone and as a result are prescribed multiple medications.[3] The most commonly prescribed medications were stimulants, followed closely by antipsychotics, anticonvulsants, and SSRIs.[7] Because these medications are prescribed to target specific symptoms, this review will discuss the safety and efficacy of medications grouped by symptom.

Social interaction/communication

Deficits in social interaction and social communication are symptoms necessary to make a diagnosis of ASD according to the DSM-5. Despite this, there are currently no FDA-approved medications for addressing these symptoms. However, treatments are emerging that show some promise.

Memantine, an N-methyl-D-aspartate receptor antagonist, showed significant improvements in social interactions, reductions in stereotyped behaviors, and overall improvement on the Gilliam Autism Rating Scale in an RCT of 60 children with ASD.[16] This study tested Memantine as adjunct treatment in children 14 years of age or younger compared with a control group of ASD patients, but did not evaluate for treatment-emergent side effects. Another RCT of Memantine showed no significant side effects in the treatment group compared with placebo. However, symptom improvement was no different than placebo.[17] These trials indicate that Memantine may be a well-tolerated and safe medication to use in the ASD population, but its viability in improving symptoms remains undetermined.

Another medication with potential to improve social functioning for ASD patients is Oxytocin. Growing evidence shows that reduced oxytocinergic function may contribute to reduced social interaction and communication in ASD patients.[18] As a result of these findings, synthetic oxytocin has emerged as a possible treatment for the social deficits associated with ASD.[19] Results from RCTs show conflicting evidence for the efficacy of oxytocin to improve social challenges in these patients. A study conducted by Dadds et al.[20] found no improvement in emotion recognition, repetitive behaviors, eye contact, or quality of social interactions in a double-blind, placebo-controlled study of 38 children with ASD. Anagnostou et al.[21] found some evidence for improvements in emotion recognition and a broad measure of quality of life in adults with ASD after receiving treatment with oxytocin.

Despite mixed evidence for oxytocin's efficacy in treating social deficits of ASD, neither study found significant side effects or issues tolerating oxytocin, as compared with placebo, in adults or children.[20,21] As with Memantine, these trials indicate that oxytocin may be a well-tolerated and safe medication for ASD, but efficacy remains undetermined.

At the date this review was written, two medications, Balovaptan[22] and Bumetanide,[23] are undergoing phase 3 trials for use in patients with ASD to address core symptoms, specifically social interaction and communication. The phase 2 clinical trial of balovaptan demonstrated no significant improvement in social responsiveness when compared with placebo after

12 weeks; however, measures of communication, socialization, and daily living skills showed improvement when compared with placebo, and this relationship strengthened with higher doses.[24]

Similar results were demonstrated in the phase 2 trial for bumetanide; no significant improvement in social responsiveness when compared with placebo, however improvement was seen in the secondary measure of repetitive behaviors.[25] Balovaptan was found to have no serious side effects and was well tolerated by the study participants; however, bumetanide was found to have some adverse effects related to the diuretic effects of the medication, orthostatic hypotension, and hypokalemia, but neither affected treatment outcomes[24,25]

Repetitive behavior/interests/activities

Repetitive behaviors have been the target of most pharmacologic treatments as they are often considered to be one of the most problematic symptoms.[26] SSRIs are often prescribed for this purpose in the ASD population and numerous studies have been published. These studies present mixed results for the safety and efficacy of any SSRI to treat these symptoms.

A national survey by Coleman et al.[7] found fluoxetine and sertraline as the most commonly prescribed SSRIs, both showing a positive self-reported benefit to risk score. However, the most commonly mentioned adverse events included aggression, anxiety, irritability, and depression, which are among the most troubling ASD symptoms.

Fluoxetine was found to reduce repetitive behaviors compared with placebo in children, but had no significant effect in reducing global autism severity.[27] This study also reported no significant differences between overall frequencies of side effects experienced in the fluoxetine treatment group versus placebo. However, the treatment group did report more sedation (17.9% vs. 11.1%), agitation (46.2% vs. 44.4%), and anorexia (15.4% vs. 11.1%) than those in the placebo group. A study testing fluoxetine use in adult ASD patients found it to be effective in reducing compulsions and improving the global autism score when compared with placebo.[28] Similar to the study with fluoxetine use in children, there was no significant difference in side effects between treatment and placebo groups, although one patient receiving fluoxetine did report suicidal ideation versus none in the placebo group.[28]

A large RCT investigating the effectiveness of the SSRI citalopram in children with high levels of repetitive behavior found no difference between treatment and placebo groups for repetitive behaviors or global autism improvements.[29] Additionally, citalopram use was associated with more frequent adverse events, with 97.3% reporting at least one treatment-emergent adverse event versus 86.8% of the placebo group ($p=0.03$).

The most common adverse events in the citalopram group were increased energy level (38.4% vs. 19.7% in placebo group), stereotypy (11.0% vs. 1.3%), impulsiveness (19.2% vs. 6.6%), decreased attention (12.3% vs. 2.6%), hyperactivity (12.3% vs. 2.6%), difficulty falling asleep (23.3% vs. 9.2%), and dry skin (12.3% vs. 1.3%).[29] Two children in the citalopram group also experienced seizures. One child required hospitalization due to prolonged seizure with loss of consciousness and continued frequent seizures despite discontinuation of treatment. The other had a history of seizures and was able to continue the trial after addition of an anticonvulsant medication.[29]

In general, SSRIs have mixed efficacy in the ASD population. Fluoxetine appears to be generally safe and effective, although many still reported adverse effects.[27] Sertraline is the other most commonly prescribed SSRI, but there are no studies available evaluating its efficacy in reducing stereotypy or improving global autism scores. Citalopram, another SSRI, appears to be no more effective than placebo and is not prescribed as often as fluoxetine or sertraline.[7]

Irritability, aggression, and agitation

Two antipsychotics, risperidone and aripiprazole, have been FDA approved to manage irritability associated with ASD.[6] While both medications have shown efficacy in this population, they also cause frequent side effects.[30–32]

Risperidone has shown significant improvements for irritability and hyperactivity in children and adolescents when compared with placebo.[33] Treatment-related adverse effects were consistent with the known risperidone profile, including increased appetite, sedation, somnolence, and increased weight.[34] Adverse events that led to discontinuation included one case of aggression in the placebo group and one case of sedation in the risperidone group.[33]

Dangerous metabolic adverse effects can occur with antipsychotics. Scahill et al.[35] examined the effects of risperidone on appetite, weight, body mass index (BMI), waist circumference, and indices associated with metabolic syndrome and insulin resistance over a 24-week period. Growth curve analysis showed an increased in BMI from pretreatment to study conclusion,

and this effect was greater for those with increased appetite in the first 8 weeks. Significant increases were also seen in glucose levels, hemoglobin A1c, insulin, homeostatic model assessment-insulin resistance, alanine aminotransferase, and leptin by week 16.[35]

Aripiprazole has shown significant improvements in caregiver-rated and clinician-rated irritability, when compared with placebo.[31] Similar to risperidone, side effects can be more common and severe than with other medications. In the Marcus et al.[31] study, 10.2% of subjects in the treatment groups discontinued aripiprazole due to adverse events, with the most common being sedation ($n=7$), drooling ($n=4$), and tremor ($n=4$). These effects were not reported in the placebo group.

A study investigating the safety and tolerability of aripiprazole in pediatric ASD patients by Robb et al.[5] found most adverse events to be mild to moderate in severity, occurring early in treatment, and generally, other than weight gain, resolving with time. The most common adverse events seen in the aripiprazole group versus placebo included sedation (20.8% vs. 4.0%), fatigue (16.5% vs. 2.0%), vomiting (13.7% vs. 6.9%), increased appetite (12.7% vs. 6.9%), tremor (9.9% vs. 0.0%), and weight gain (mean 1.6 kg vs. 0.4 kg).

Some anticonvulsant medications have been found to be effective in treating irritability in children with ASD. Based on caregiver and clinician-rated scales, valproic acid (Depakote) was found to improve irritability compared with placebo.[36] The study was not sufficiently powered to identify side effects of treatment versus placebo.

Oxcarbazepine is another anticonvulsant prescribed to ASD patients to treat irritability.[7] A retrospective study by Douglas et al.[37] found that 47% of participants experienced improvements according to a clinician-rated irritability scale. However, many adverse events were observed, with 23% of patients stopping treatment as a result. These ranged from worsened irritability in four cases to hyponatremia and seizures in one case. Many ASD patients have comorbid epilepsy, thus drugs such as Depakote or oxcarbazepine are used to treat both irritability and seizures.[3] This will be discussed in greater detail in Seizures section.

Hyperactivity, attention, and cognition

ADHD symptoms are prevalent in children and adolescents with ASD and contribute to significant functional challenges.[6] Stimulants are often prescribed as they have been found to be effective in treating hyperactivity and impaired attention and cognition in the general population. However, more side effects and lower efficacy are seen in the ASD population compared with neurotypical youth with ADHD.[6,7]

A meta-analysis of data from four studies evaluating high-dose methylphenidate (stimulant) use in the ASD population found significant reductions in hyperactivity and inattention.[38] An additional RCT of methylphenidate versus placebo similarly displayed improvement of hyperactivity with medium and high doses.[39] Reported side effects were minimal, with the only significant difference between treatment and placebo being reduced appetite and insomnia.[38] However, the results of a national survey report high rates of methylphenidate side effects, including aggression, irritability, reduced appetite, and sleep problems.[7]

Another medication often prescribed to ASD patients for hyperactivity and attention deficit is atomoxetine (selective norepinephrine reuptake inhibitor). In a study by Harfterkamp et al.[40] improvements in hyperactivity and inattention were shown to be significant ($p<0.001$), when compared with placebo, in children with ASD receiving treatment with atomoxetine. Adverse events seen more by the atomoxetine treatment group as compared with placebo were nausea (29.2% vs. 8.2%), decreased appetite (27.1% vs. 6.1%), and early morning awakening (10.4% vs. 0.0%). Additionally, one patient in the atomoxetine group discontinued treatment due to fatigue versus none in the placebo group. These results are similar to another study evaluating atomoxetine use in the ASD population, which specified benefits as improvement of hyperactivity and inattention and side effects as irritability, nausea, and fatigue.[41]

Guanfacine (alpha2A-adrenergic receptor agonist) was FDA approved in 2009 to treat ADHD in the general population for ages 6–17 and has been prescribed to ASD patients for hyperactivity and inattention as well.[42] Guanfacine has been shown to be superior to placebo for both caregiver-rated and clinician-rated hyperactivity ($p<0.001$).[43] However, guanfacine was found to cause more frequent adverse events when compared with placebo: drowsiness (86.7% vs. 9.4%), fatigue (63.3% vs. 9.4%), decreased appetite (43.3% vs. 6.3%), irritability (36.7% vs. 9.4%), anxiety (30% vs. 3.1%), and mid-sleep awakening (30% vs. 6.3%). One serious adverse event was reported. A patient in the treatment group became verbally and physically aggressive, requiring police involvement, subsequent inpatient psychiatric hospitalization, and discontinuation of guanfacine treatment.[43]

Seizures

Currently the FDA[44] has approved one cannabis-derived pharmaceutical for use in the pediatric population. Epidiolex is a cannabidiol (CBD)-derived oral solution for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome, two rare and severe forms of epilepsy. The prevalence of comorbid epilepsy is ~12% in childhood and 26% in adolescence in ASD patients.[45] The pathophysiology of both ASD and epilepsy share several synaptic plasticity pathways.[46] Although not FDA approved to address such symptoms, many antiepileptic drugs are prescribed for irritability or emotional regulation in ASD, due to their stabilizing and sedative properties.

In a 2009 survey conducted by the Autism Research Institute,[47] the antiepileptic drugs (AEDs) Depakote and carbamazepine showed net benefits for both seizures and behavioral symptoms. In contrast, adverse side effects outweighed benefit for the AEDs, clonazepam and diazepam. Similarly, a review of seizure medications for the ASD population found Depakote to be effective for both seizures and behavioral symptoms, whereas carbamazepine, clonazepam, and lamotrigine effective for seizures only.[48] The anticonvulsant oxcarbazepine and antiseizure medication, gabapentin, were both minimally effective for seizures, with no benefit for behavioral symptoms.

Sleep problems and anxiety

Sleep problems and anxiety are common comorbid diagnoses in the ASD population, appearing in 50–80% and 42–56%, respectively.[4] Common management techniques for sleep often focus on nonpharmacologic methods, such as establishing bedtime routines and promoting positive sleep patterns for young children.[49] Melatonin has been used as a pharmacologic option. A study by Andersen et al.[50] found eradication of sleep problems in 25%, improved sleep in 60%, and no change in 13% of 107 children with ASD using melatonin. Of note, only three children experienced side effects, morning sleepiness, and increased enuresis, and no patients experienced increased or new-onset seizures.

In support of these findings, a meta-analysis of 18 studies measuring melatonin use in the ASD population by Rossignol and Frye[51] found significant improvements in sleep duration and sleep onset latency when compared with placebo. Additionally, a 2019 systematic review of drug interventions for sleep disorders in children with ASD found melatonin to significantly improve sleep latency, total sleep time, reduced insomnia symptoms, and was a safe long-term treatment option for children with ASD and insomnia.[52]

Anxiety symptoms are typically managed by SSRIs in the ASD population with varying efficacy and sometimes with concerning side effects such as increased anxiety and agitation.[7] A study by Thorkelson et al.[53] measured the effect of monotherapy with the SSRIs sertraline, citalopram, or fluoxetine specifically for improvement of anxiety in 29 ASD children and adolescents. Overall, 55.2% of patients experienced improvement of symptoms after 7–12 months on the same SSRI and 13.8% experienced no change or worsening of anxiety symptoms. Seven patients reported treatment-related side effects of vivid dreams, increased emotional lability, and irritability, and four patients discontinued treatment before study conclusion.[53]

Biologic Plausibility of Cannabis as a Treatment Option for ASD

Currently, we do not possess a clear understanding of the fundamental pathophysiology or etiology of ASD. Although progress has been made identifying genetic or environmental factors, difficulties still remain surrounding development or investigation of possible treatments.[54] However, recent studies have shown a link between ASD and the endocannabinoid system.[55–57] The endocannabinoid system comprises lipid neuromodulators produced in the body, and their cellular receptors. These endogenous cannabinoids (eCBs) regulate synaptic transmission in nerve cells and play an important role in many behavioral functions.[56]

Cannabis produces physiologic effects mainly through action by Δ9-tetrahydrocannabinol (THC) and CBD at the same receptors as eCBs, cannabinoid type 1 receptor (CB1R).[58] More specifically, THC has high affinity at CB1R, whereas CBD is an allosteric modulator of CB1R, potentially decreasing the effects of CB1R agonists such as THC, and inhibits the enzyme fatty acid amide hydrolase (FAAH) leading to increased levels of eCBs and eCB-like molecules; anandamide (AEA), n-palmitoylethanolamine (PEA) and N-oleoylethanolamine (OEA).[59,60]

Studies have shown links between the endocannabinoid system and ASD-specific symptoms. Karhson et al.[60] proposed a role for dysregulated cannabinoid signaling in the pathophysiology of the social functioning deficits seen in many brain disorders, including ASD. Supporting this, several animal studies have demonstrated improvements in social functioning through

enhanced AEA signaling by inhibition of its breakdown and increased action at CB1R.[55,61] Additionally, FAAH breaks down AEA (and structurally related compounds, PEA and OEA) leading to decreased concentrations at CB1R and CB2R; while inhibiting FAAH increases levels of AEA, suggesting FAAH may be a novel therapeutic target for ASD.[55]

Karhson et al.[56] conducted the first study to translate these preclinical findings into useful information for human ASD patients. They found that AEA concentrations were lower in the ASD population than in a control population of neurotypical children. A twofold increase in AEA corresponded with a fourfold decrease in the likelihood of ASD. In support of these findings, a 2019 study by Aran et al.[57] found that serum levels of AEA, PEA, and OEA were lower in children with ASD compared with an age, gender, and BMI-matched control group. Furthermore, AEA levels were not statistically associated with age, gender, BMI, medications, or ADHD status, but remained independently associated with ASD status.[57]

These findings suggest low circulating eCBs as a possible biomarker for ASD, providing a potential method for earlier diagnosis. This is of great significance due to the heterogeneity of the disorder and the importance of early behavioral intervention in improving long-term outcomes.[1,57]

In addition, some studies have shown an association between cannabinoids in the neurotypical population and sleep and anxiety. Endocannabinoids have been found to exhibit a circadian rhythm, implicating their association with sleep.[62] A study by Nicholson et al.[63] found cannabinoids to have varying benefits on sleep for neurotypical patients and rarely adverse clinical effects related to sleep. Additionally, various studies have shown improvement of sleep problems with the use of cannabinoids for patients with chronic pain.[64–66] The eCB system has been implicated to mediate anxiety through CBD action at CB1R in the brain.[67] A supportive study, which used CBD for social anxiety disorder, demonstrated improvements in anxiety, cognitive impairment, and discomfort during simulated public speaking.[68]

Cannabis and ASD

Therapeutic effects

As of the date this review was written, there has been one proof-of-concept randomized trial by Aran et al.[69] showing that a 20:1 CBD:THC cannabis product is well tolerated for 3 months in ASD patients. There is also another randomized double-blind clinical trial studying the efficacy and safety of cannabidivarin in children with ASD (https://clinicaltrials.gov/ct2/show/NCT03202303). All other evidence provided about this topic comes from the limited number of existing cohort studies; primarily four studies which had a treatment group, but no comparative control group. These studies all measured response to CBD-rich medical cannabis in diagnosed ASD patients for various categories of symptoms, comorbidities, and side effects.

Aran et al.[70] performed a retrospective study assessing the efficacy and safety of CBD-rich cannabis in 60 children with ASD and severe behavioral concerns. These patients received sublingual oil of whole plant extracts containing CBD and THC in a 20:1 ratio for 7–13 months. Anxiety was "very much improved" or "much improved" in 39% of patients, communication was "very much improved" or "much improved" in 47% of patients, and behavioral problems were "very much improved" or "much improved" in 61% of patients. This study did not evaluate cannabis' effects on sleep problems or seizures.

A prospective study by Bar-Lev Schleider et al.[71] measured response to 20:1, CBD:THC medical cannabis in 93 ASD patients specifically for improvement of agitation and common comorbid symptoms of ASD after 6 months of use. Improvement with outbursts and agitation was reported in 90.3% and 85.2% of participants, respectively. However, 9.5% and 14.7% saw no change or worsening of symptoms, respectively. Positive mood was also found to be improved from 42% of patients at baseline, to 63.5% after receiving treatment.

This study also measured changes in comorbid symptoms of ASD: hyperactivity/restlessness, cognition, attention, seizures, sleep problems, and anxiety. At study commencement, 90.4% of patients reported issues with restlessness, 48.4% reported issues with cognitive impairment, and 0.0% reported good concentration with daily tasks.[71] After 6 months of treatment, 91.0% experienced improvement of restlessness, 27.2% saw improvement in cognition, and 14.0% reported at least good concentration on daily tasks. Overall, 84.6% of patients with comorbid seizures experienced improvement and 15.3% experienced complete symptom disappearance after treatment with CBD-rich medical cannabis. Sleep problems were also measured, showing improvement in 78.3% of patients, where 19.5% had complete symptom disappearance. Anxiety showed improvement in 88.8% of patients, while 11.1% experienced no change or worsened anxiety.

A prospective study by Barchel et al.,[72] also using 20:1 CBD:THC medical cannabis, compared outcomes in 53 ASD patients with outcomes seen with commonly used pharmaceuticals. This study focused on comorbid symptoms, such as outbursts/self-injury, hyperactivity, sleep problems, and anxiety.

Outbursts and self-injury were experienced by 34 patients at study initiation and were found to be improved in 67.6%, no change in 23.5%, and worsened in 8.8% with CBD-rich cannabis. These results were compared with those of aripiprazole seen in the study by Marcus et al.[31] Cannabis showed greater improvement in outbursts and self-injury than aripiprazole and there was no difference in worsening effects.[72] Of the 38 children with hyperactivity symptoms, 68.4% saw improvement after receiving treatment and 2.6% saw worsening of symptoms. This improvement was on par with traditional treatment with methylphenidate according to a study by Handen et al.[73]

Additionally, the study on CBD-rich cannabis found that 71.4% of patients experienced improved sleep, 23.8% saw no change, and one patient had worsened symptoms.[72] This was not statistically different from outcomes seen with melatonin use ($p=0.400$). Anxiety improved with cannabis use in 47.1% of the 17 patients who had anxiety at study initiation. This was not statistically different from improvements seen with SSRIs ($p=0.232$).

The fourth study by Fleury-Teixeira et al.[74] observed response to using 75:1 CBD:THC cannabis extract in 18 children with ASD for 9 months. Results were collected monthly through guardians or caretakers completing questionnaires on the estimated severity of eight symptom categories: ADHD symptoms, behavioral disorders, motor deficits, autonomy deficits, communication and social interaction deficits, cognitive deficits, sleep disorders, and seizures. Of the 15 patients that completed the treatment plan, 60% of patients saw improvements of 20% or more in ADHD symptoms, motor deficits, communication and social interaction, behavioral disorders, sleep disorders, and seizures. The most significant improvements were seen in ADHD symptoms, sleep disorders, and seizures, with 80% of participants having improvements equal or greater than 30%.[74]

Of note, a number of patients in these studies stopped using other medications. In the study by Aran et al.,[70] 49 children were using medications and cannabis concomitantly at the beginning. However, by study conclusion, 33% had lowered the dose of their medications, 24% completely discontinued medications, and only 8% increased dose of medications. Similarly, Bar-Lev Schleider et al.[71] reported that of the 67 patients who were taking medications at onset of the study, 34.3% decreased or stopped concomitant medication use and only 8.9% received higher doses of medications after introduction of cannabis. Of the 10 patients taking neuropsychiatric medications at study onset for Fleury-Teixeira et al.,[74] 8 patients were able to decrease or discontinue use of these medications. Barchel et al.[72] did not report concomitant medication use or discontinuation of medications.

Side effects

As with the other commonly prescribed medications for ASD, it is important to mention side effects experienced during treatment with medical cannabis. Aran et al.[70] found sleep disturbances resulting from hypervigilance in 14% of patients as the most common side effect. However, these symptoms resolved in most patients by altering the evening dose given. Other common side effects were restlessness, nervousness, and loss of appetite, all seen in 9% of patients.

Results from Bar-Lev Schleider et al.[71] showed similar results, with the most common side effect being restlessness in 6.6% of patients and somnolence, psychoactive effect, and increased appetite appearing in 3.2% of patients each. Barchel et al.[72] found the most reported side effects being somnolence in 22.6% of patients and changes in appetite in 18.9%. Finally, Fleury-Teixeira et al.[74] reported sleepiness and moderate irritability as the most common adverse effect experienced in three patients.

Other important measures include the number of patients who maintained treatment with medical cannabis, the number that discontinued use, and their reasoning. Retention rates in all studies were high with 73% of patients still using medical cannabis in the study by Aran et al.,[70] 86.6% in the study by Bar-Lev Schleider et al.,[71] and 83.3% in the study by Fleury-Teixeira et al.[74] The most commonly cited reason for discontinuing treatment was low efficacy, followed closely by side effects.[70–72]

According to Aran et al.,[70] 16 children (27%) stopped treatment for the following reasons: a combination of low efficacy and side effects ($n=7$), low efficacy ($n=5$), irritability when beginning treatment ($n=2$), unsuccessful administration of treatment ($n=1$), and transient psychotic event ($n=1$). Bar-Lev Schleider et al.[71] cited 23 patients discontinuing treatment. Seventeen provided explanation for discontinuation: 12

discontinued due to low efficacy and 5 due to side effects. However, seven patients stated they intended to return to the treatment. The Barchel et al.[72] study lost five families to follow-up. Two stopped treatment because of low efficacy, two continued treatment but changed their medical cannabis provider, and one patient's license for medical cannabis expired. Across all three studies, only one serious adverse event led to discontinuation of medical cannabis, the transient psychotic episode in an adolescent girl.[70]

Risks of Cannabis Use

Youth

Cannabis use among adolescents and children remains controversial due to possible physical and mental health consequences, especially as children are still developing.[75] Of importance to the ASD population are investigations on cannabis' effects on cognition and psychosis as these are the main risks studied regarding cannabis use in youth. Typically, this implies the use of recreational cannabis, which is traditionally high THC with very low CBD levels, in contrast to studies in the ASD population, which typically use high CBD, low THC products.

Evidence has shown clear acute cognitive effects after recreational cannabis use. However, a more relevant outcome of interest is the residual cognitive effects. Several studies have found an association between adolescent recreational cannabis use and cognitive and academic impairment lasting up to 28 days after last use.[76–78] Findings have indicated a potential linear relationship between the frequency of recreational cannabis use and performance on cognitive function tests; showing adolescents with higher lifetime use scoring lower. However, a recent meta-analysis by Scott et al.[75] found no significant difference in cognitive function between recreational cannabis users and nonusers after an abstinence period of at least 72 h since last use ($d = -0.08$, 95% CI -0.22 to 0.07; $p = 0.29$).

Current research has provided substantial evidence that adolescents who use cannabis daily or near-daily are more likely to develop future psychotic disorders than nonusers.[79–81] In a longitudinal cohort study of over 6000 participants, 5 or more instances of cannabis use by age 15–16 was associated with greater odds of psychotic disorder by age 30 (adj OR 3.02, 95% CI 1.14 to 7.98).[80] Research has also displayed evidence that adolescent cannabis users are more likely than nonusers to develop future psychotic symptoms, and this increases with more frequent use and is directly related to THC concentration.[79,82,83] However, it remains unclear how cannabis may interact with other risk factors for psychosis, particularly within the ASD population.

Adult

Research has failed to show an association between less-than-weekly cannabis use in adults and psychotic symptoms or disorders.[84] However, substantial evidence has been found indicating that THC intoxication in adults can cause acute psychotic symptoms, following a positive linear correlation with higher doses.[85,86] A study by Di Forti et al.[87] found that individuals who smoked every day had 3.04 (95% CI 1.91 to 7.76) greater odds of having first episode psychosis compared with those who had never used cannabis.

Research has not shown long-term cognitive impairment in adults associated with cannabis use. A meta-analysis found neurocognitive performance in cannabis users to be no different than nonusers after 28 days of abstinence.[88]

Discussion

Diagnostic criteria for ASD have been established, yet difficulties still remain when diagnosing and appropriately treating patients due to the heterogeneity of the disorder. Patients can present with great variability in core symptom severity along with many common comorbidities, such as epilepsy, sleep disorders, ADHD, intellectual disability, and many other psychiatric or medical comorbidities. The heterogeneity of ASD produces great difficulties in appropriately treating this disorder, leading to many medication changes or treatment trials throughout the patient's life.

Currently, only two medications are FDA approved for use in the ASD population, risperidone and aripiprazole, to target comorbid irritability, yet numerous other medications are commonly prescribed in an attempt to control core symptoms or common comorbid symptoms associated with ASD. Common medications have varying levels of efficacy, safety, and tolerability between patients. Social deficits are one of the diagnostic symptoms of ASD. Medications currently prescribed to manage these challenges, Memantine and oxytocin, show mixed results, but appear safe and tolerable.

Another component of symptoms necessary for diagnosis are repetitive behaviors, interests, or activities, which are typically targeted by SSRIs. However, mixed results from various trials indicate that SSRIs have questionable tolerability and safety for use by children or adolescents. Some of the most common side effects cited are

also considered the most troubling symptoms associated with ASD: aggression, anxiety, irritability, depression, weight gain, and negative effects on cognition.

Stimulants are often prescribed to treat comorbid hyperactivity, inattention, and deficits in cognition. While often effective, efficacy and tolerability appear lower in the ASD population than in neurotypical youth. Antipsychotics have proven effective for irritability associated with ASD, however, their safety and tolerability remain questionable, with many patients discontinuing use as side effects often outweigh benefits.

Finally, many patients are prescribed anticonvulsant medications due to the high prevalence of comorbid seizures and in an attempt to control irritability and aggression associated with ASD. Although effective for seizures, benefits regarding behavioral symptoms are mixed. Valproate, however, was uniquely effective for both. Due to the heterogeneity of ASD and the massive variability of medication efficacy in this population, there still remains no proven treatment option for the core symptoms. Additionally, many medications induce side effects that outweigh benefits, and in some cases, perpetuate the most concerning ASD symptoms, such as irritability and aggression.

Recent cohort studies have displayed the potential efficacy, safety, and tolerability of CBD-rich medical cannabis use for treating both core symptoms of ASD and many comorbid symptoms, such as irritability and sleep problems. In support of these findings, some studies have suggested a biologic plausibility behind cannabis due to interactions with the endocannabinoid system. These studies have shown CBD acting as an allosteric modulator to CB1R and inhibiting breakdown of eCBs, which have been found in lower concentrations in the ASD population. Additionally, CBD has been shown to exert its effects in neuropsychiatric disorders through non-CB1 receptors, such as serotonin 5-HT1A, glycine $\alpha 3$ and $\alpha 1$, TRPA1, TRPV1, GPR55, GABAA, PPARγ, and by inhibiting adenosine reuptake.[89–92]

Circulating eCBs have also been identified as a possible biomarker for ASD, providing a possible new method of diagnosis, which would improve long-term outcomes as patients could be identified at a younger age. Further support of CBDs potential in ASD patients can be found in three randomized placebo-controlled trials measuring the effect of CBD on brain connectivity and excitation and inhibition systems through magnetic resonance spectroscopy in adults with and without ASD.[93–95]

Results displayed CBD significantly altered functional connectivity in brain regions implicated in ASD, with no significant change in the control population.[93] More specifically, CBD altered excitatory glutamate response in ASD and control participants, but only altered inhibitory GABA pathways in ASD participants.[94] These findings suggest a theoretical pathophysiological mechanism for CBD as a possible treatment option for ASD and support the rationale for current, ongoing clinical trials of cannabis use in the ASD population.[70]

With the increased interest in medical cannabis among the ASD population, more patients or their caretakers will likely seek advice from physicians. However, an Association of American Medical Colleges (AAMC) survey found 75% of medical school dean's reporting that graduates are either slightly prepared or not at all prepared to answer patients' questions about medical cannabis.[96]

Additionally, current recommendations from American Academy of Pediatrics (AAP) on complementary health approaches (such as medical cannabis) are to monitor use with questionable effectiveness and discourage use in those with proven health risks.[97] Specifically regarding cannabis, the AAP opposes medical cannabis use for children, except in situations "that pertain to emerging anecdotal information concerning the medical potential of cannabinoid medications, which may be an option for children who have life-limiting or severely debilitating conditions and for whom current therapies are inadequate."[98]

These recommendations are difficult to interpret and it could be argued that ASD can be life limiting and severely debilitating for some patients. Hopefully with completion of RCTs and continued reports displaying efficacy and tolerability of medical cannabis as a treatment option for ASD, more physicians will feel prepared to discuss cannabis with, and possibly implement as a treatment choice for, their patients.

Of concern is the safety of medical cannabis use among children with ASD. Current studies have shown cognitive impairment and possible psychotic symptoms resulting from recreational cannabis use during childhood or adolescence; however, the magnitude of effect remains questionable. THC has been determined to cause acute psychotic symptoms, whereas CBD has been shown to have no psychoactive properties and to inhibit the psychotomimetic effects of THC.[59,85] It is imperative to note that currently, recreational cannabis products are not regulated based on THC to CBD ratios, unlike the compounds that have been used in current ASD medical cannabis research, which often contain a 20:1 ratio of CBD to THC.

As with current treatment options for ASD patients, providers must take into consideration the patient's history, severity of symptoms, and the established safety and efficacy behind any treatment being considered. However, CBD-rich medical cannabis has shown to be a relatively safe and well-tolerated option to relieve several behavioral and comorbid symptoms of ASD, such as seizures, sleep problems, and irritability. Taking into consideration the risks associated with adolescent recreational cannabis use and the possible efficacy of medical cannabis for the ASD population, as suggested by uncontrolled case series, the benefits may outweigh the risks for many patients.

This review has several limitations. Searches performed were restricted to English-language publications accessed through PubMed, PubMed Central, or Google Scholar. Many studies included regarding commonly used medications only tested for certain side effects or benefits, limiting generalizability to the broader ASD population. All studies included regarding medical cannabis were cohort studies or reports, limiting the strength of conclusions made. Additionally, participation bias may be present regarding medical cannabis use as those in support may be more inclined to participate.

Conclusions

Due to the heterogeneity of ASD, difficulties remain surrounding effective treatment, with many options available, varying in efficacy and safety depending on the symptoms targeted and patient themselves. Some of the most commonly prescribed medications show a risk of side effects and potential to perpetuate troubling symptoms of ASD, like irritability.

Recent studies have found links between the endocannabinoid system and symptoms of ASD, establishing a potential role as a biological marker for ASD and as a target for treatment of ASD symptoms. Furthermore, biologic plausibility for CBD-rich cannabis as an effective and tolerable treatment option for ASD patients has been recently suggested by several reports and studies, however, no completed placebo-controlled studies support this. However, as with other treatments for ASD, cannabis has shown a variation in its effects between different symptoms and patients, so its use may not be recommended for everyone and should be monitored closely by a physician.

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Abbreviations Used

AAMC = Association of American Medical Colleges
AAP = American Academy of Pediatrics
ADHD = attention-deficit/hyperactivity disorder
AEA = anandamide
AEDs = antiepileptic drugs
ASD = Autism Spectrum Disorder
BMI = body mass index
CB1R = cannabinoid type 1 receptor
CBD = cannabidiol
CI = confidence interval
DSM-V = Diagnostic and Statistical Manual of Mental Disorders, fifth edition
eCBs = endogenous cannabinoids
FAAH = fatty acid amide hydrolase
FDA = Food and Drug Administration
MeSH = medical subject heading
OEA = N-oleoylethanolamine
OR = odds ratio
PEA = n-palmitoylethanolamine
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT = randomized controlled trial
SSRIs = selective serotonin reuptake inhibitors
THC = Δ9-tetrahydrocannabinol

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Medical cannabis for the treatment of comorbid symptoms in children with autism spectrum disorder: An interim analysis of biochemical safety

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Background: Autistic Spectrum Disorder (ASD) is a common neurodevelopmental disorder and no effective treatment for the core symptoms is currently available. The present study is part of a larger clinical trial assessing the effects of cannabis oil on autism co-morbidities.

Objectives: The aim of the present study was to assess the safety of a CBD-rich oil treatment in children and adolescents with ASD.

Methods: Data from 59 children and young adults (ages 5–25 years) from a single-arm, ongoing, prospective, open-label, one center, phase III study was analyzed. Participants received the Nitzan Spectrum® Oil, with cannabis extracts infused in medium chain triglyceride (MCT) oil with a cannabidiol: THC ratio of 20:1, for 6 months. Blood analysis was performed before treatment initiation, and after 3 months. Complete blood count, glucose, urea, creatinine, electrolytes, liver enzymes (AST, ALT, gamma glutamyl transferase), bilirubin, lipid profile, TSH, FT4, thyroid antibodies, prolactin, and testosterone measurements were performed at baseline, prior to starting treatment and at study midpoint, after 3 months of treatment.

Results: 59 children (85% male and 15% female) were followed for 18 ± 8 weeks (mean ±SD). The mean total daily dose was 7.88 ± 4.24 mg/kg body weight. No clinically significant differences were found in any of the analytes between baseline and 3 months follow up. Lactate dehydrogenase was significantly higher before treatment (505.36 ± 95.1 IU/l) as compared to its level after 3 months of treatment (470.55 ± 84.22 IU/L) (p = 0.003). FT4 was significantly

higher after 3 months of treatment (15.54 ± 1.9) as compared to its level before treatment (15.07 ± 1.88) (p = 0.03), as was TSH [(2.34 ± 1.17) and (2.05 ± 1.02)] before and after 3 months of treatment, respectively (p = 0.01). However, all these values were within normal range. A comparison of the group with additional medications (n = 14) to those who received solely medical cannabis (n = 45) showed no difference in biochemical analysis, including liver enzymes, which remained stable, except for change in potassium level which was significantly higher in the group that did not receive additional medications (0.04 ± 0.37) compared to the group receiving concomitant drug therapy (-0.2 ± 0.33) (p = 0.04). A comparison of patients who received a high dose of the cannabis oil (upper quartile-16 patients), with those receiving a low dose (lower quartile—14 patients) showed no significant difference between the two groups, except for the mean change of total protein, which was significantly higher among patients receiving high dose of CBD (0.19 ± 2.74) compared to those receiving a low dose of CBD (1.71 ± 2.46 (p = 0.01), and mean change in number of platelets, that was significantly lower among patients who received high dose of CBD (13.46 ± 31.38) as compared to those who received low dose of CBD (29.64 ± 26.2) (p = 0.0007). However, both of these changes lack clinical significance.

Conclusion: CBD-rich cannabis oil (CBD: THC 20:1), appears to have a good safety profile. Long-term monitoring with a larger number of participants is warranted.

KEYWORDS

biochemical safety, cannabis, medical, autism spectrum, disorder, pediatric

1 Introduction

Autistic Spectrum Disorder (ASD) is a neurodevelopmental disorder that includes a wide range of complex developmental disabilities. The core symptoms of autism include impairments in social interaction and communication, as well as the presence of restricted and repetitive behaviors (APA, 2013). Despite its prevalence among the common neuro-biological-based childhood disorders, no effective treatment for the core symptoms of ASD is currently available, and to date, the standard of care consists primarily of behavioral interventions (Zamberletti et al., 2017). The only two medications currently approved by the FDA for the indication of irritability in children with ASD are risperidone and aripiprazole. In clinical practice, physicians often prescribe other drugs such as SSRI's and methylphenidate off label, to treat the behavioral and social deficit related co-morbidities of ASD, and the effects of these medications are inconsistent (Lai et al., 2014).

One of the newer treatment options being investigated for ASD, as well as an array of other conditions, is cannabidiol (CBD)-rich cannabis extract (Barchel et al., 2019; Aran and Rand, 2020; Ponton et al., 2020). Conditions such as anorexia, emesis, pain, inflammation, multiple sclerosis, neurodegenerative disorders (Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease), epilepsy, glaucoma, osteoporosis, schizophrenia, cardiovascular disorders, cancer, obesity, and metabolic syndrome-related disorders, to name a few, are also being treated or have the potential to be treated by cannabinoid agonists/antagonists/cannabinoid-related compounds (Schlag, 2020).

Cannabis contains a number of active compounds, including Δ9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD) and terpenoids (Russo, 2011). CBD has anti-emetic, anti-convulsive, anti-psychotic, anti-inflammatory, antioxidant and neuroprotective properties (Cheng et al., 2014) and is generally well-tolerated (Devinsky et al., 2014; Detyniecki and Hirsch, 2015). Δ9-Tetrahydrocannabinol (THC) has psychoactive and relaxant effects and often imparts a sense of euphoria, a quality which underlies its utility as a treatment for pain and nausea. Δ9-THC also activates the endocannabinoid system in the central nervous system and affects anxiety, appetite, cognitive function and memory (Palmieri et al., 2017).

Both CBD and THC bind to both the CB1/CB2 receptors in the human endocannabinoid system (ECS), with varying levels of affinity (Gallily et al., 2015).

The human endocannabinoid system, composed of endogenous, lipid-based retrograde neurotransmitters that bind to cannabinoid receptors and cannabinoid receptor proteins throughout the central and peripheral nervous system (Freitas et al., 2018) is often affected in conditions such as epilepsy, anxiety, cognitive impairments and sleep pattern disturbances (Zamberletti et al., 2017). The ECS has drawn attention in recent years as a potential contributor to ASD,

due to its role in regulation of synaptic function through its inhibition of the release of neurotransmitters from presynaptic neurons (Ponton et al., 2020).

The majority of the available data on the safe use of CBD in children is on the treatment of epilepsy, specifically FDA-approved Epidiolex® (Devinsky et al., 2017). Recently, increasing preclinical and clinical data have highlighted the therapeutic benefits of cannabinoids for individuals with ASD. Reviews which have examined the effects of cannabis types and dosages on common co-morbidities in ASD (including irritability, hyperactivity, sleep disorders, self-injurious behavior, anxiety) describe positive results (Barchel et al., 2019). Yet, despite evidence for its efficacy, concerns about adverse outcomes, such as agitation, somnolence, decreased appetite, and irritability have been raised (Agarwal et al., 2019; Poleg et al., 2019). In addition, data on the increased risk of hepatotoxicity, mainly when co-administered with valproate, have accentuated the need for further study of its biochemical safety (Samanta, 2019; Sands et al., 2019; Aran and Rand, 2020; Lattanzi et al., 2020).

The effect of medical cannabis on hormones such as prolactin, thyroid function and testosterone, should be is an under-explored area of study. In one double-blind study of 11 healthy adults, in which CBD or a placebo at doses of 300 mg or 600 mg were administered by injection, basal prolactin and growth hormone levels remained unchanged both after placebo and CBD. We have yet to identify literature which suggests CBD has any adverse effect on kidney function (Rein, 2020). As a result, the goal of the current study was to assess the biochemical safety of CBD-rich cannabis oil in children with ASD.

2 Aim and study population

The aim of this prospective cohort was to assess the safety-related blood tests of children and young adults with ASD taking a CBD-rich cannabis oil-based product. Participants were recruited during the period spanning November 14 2019 to May 25 2021. Data from a baseline sample (pre-treatment) of 59 children and young adults (ages 5–25 years) from an ongoing prospective single-arm, open-label, one center, phase 3 study was analyzed. Eligibility for inclusion in the study included a diagnosis of ASD (DSM-5) by a pediatric neurologist or a pediatric psychiatrist in the community healthcare setting. In addition, patients were required to have at least one severe co-morbidity, such as problems with sleep, aggression/self-injury behaviors, anxiety, or irritability that existed for at least 6 months. Prior to enrollment, treatment and collection of data, written informed consent was obtained from the parents of all participants. Children and adolescents with a known genetic syndrome such as tuberous sclerosis, Fragile X syndrome, and Angelman syndrome were excluded, as were those currently receiving or who had received medical cannabis therapy in the past, had current psychosis, schizophrenia or schizo-affective disorder or had a first degree relative with these disorders. Children diagnosed with a metabolic illness, immune disorder or liver cancer, or epilepsy with clinical symptoms (presence of non-clinical epileptic activity did not represent a reason for exclusion) were also excluded from participating. Ethical approval for the study was obtained from the local Helsinki committee (Number 281–17-ASF) and was registered with ClinicalTrials.gov (NCT05212493).

3 Methods

3.1 Treatment protocol

The treatment protocol was individualized for each patient using a personalized medicine approach. Participants received medical cannabis extract infused in MCT oil with a CBD:THC ratio of 20:1 (Or Nitzan Spectrum®, Seach Medical Group, Israel, manufactured by Nextage Therapeutics, Israel) for 6 months. Parents were instructed to start with one oral drop daily (each drop contains: 0.3 mg THC and 5.7 mg CBD) and increase the dosage gradually until they perceived improvements in their child's behavior such as decreased irritability, aggressiveness, hyperactivity, and/or sleep disturbances. The amount and timing of doses during each day was tailored to individual needs of the child (e.g., higher dose at night if needed for sleep support). Parents completed a bi-weekly phone interview where they reported compliance, behavior, symptoms, and side effects. The maximum dose did not exceed 10 mg/kg/day (or total of 400 mg/day) of CBD and 0.5 mg/kg/day (or total of 20 mg/day) of THC based upon previous findings (Aran and Rand, 2020). Information on comorbid symptoms and safety was recorded biweekly during follow-up interviews during the 6 month study. Participants taking any medications prior to entering the study were instructed not to make any changes during the study period.

3.2 Primary and secondary outcome measures

Medical interview was performed and weight/height measurements collected. Primary outcome measures included blood analytes which included: complete blood count, glucose, urea, creatinine, electrolytes, liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT)), bilirubin, lipid profile, thyroid stimulating hormone (TSH), free T4, thyroid antibodies, prolactin, and testosterone. CBC was measured in whole blood and all other biochemistry parameters were

TABLE 1 Patients characteristics and baseline symptoms.

Characteristics		
Sex, n (%)	Male	50 (84.7)
	Female	9 (15.3)
Age (years), mean (STD, range)		10.7 (4.6, 5–25)
Concomitant drugs, n (%)	No	45 (76.2)
	Yes	14 (23.8)
Medications, n (%)	Stimulants	6 (10.2)
	Typical antipsychotics	2 (3.4)
	Atypical antipsychotics	6 (10.2)
	Anti-epileptic	2 (3.4)
	Melatonin	5 (8.5)
	Anti-depressant	2 (3.4)
	Other anti-muscarinic	1 (1.7)
	Alpha agonist	1 (1.7)
Mean CBD Daily dose per mg/kg		2.75 (1.30)

measured in the serum using Cobas® 8000 analyzer (Roche Diagnostics). Blood tests were performed in the morning, at baseline, prior to starting treatment and at study midpoint, after 3 months of treatment. Secondary outcomes were change in safety tests both with varying doses of CBD as well as with concomitant drug usage.

3.3 Study procedure

Baseline–All participants underwent a medical history and physical exam, completed questionnaires and underwent blood testing, growth measurements, EEG, Autism Diagnostic Observation Schedule (ADOS), Vineland adaptive behavior scales, and cognitive tests.

Follow up—Biweekly during follow-up interviews by telephone were conducted throughout the study. At midpoint (3 months), an in person interview was conducted and blood work and growth indices were taken. After 6 months, growth measurements, ADOS, EEG, Cognitive and Vineland adaptive behavior scales were completed.

3.4 Statistical analysis

Data is presented as mean and standard deviation for continuous variables and percentage of frequency for categorical variables. Blood count and biochemical blood tests were tested before and after treatment using paired *t*-test. Unpaired *t*-test was utilized in two secondary analyses. The first analysis examined the differences before and after CBD treatment in patients treated with co-medications versus patients who were not exposed to other medications; the second analysis compared the differences before and after treatment in patients exposed to high CBD dosage (dose belongs to the upper quartile, i.e. 3.51–6.53 mg/kg per day) versus patients exposed to low CBD dosage (dose belongs to the lowest quartile, i.e. 0.71–1.78 mg/kg per day). Data was analyzed with "PANDAS" and "Scipy" packages in python via the platform of Jupyter notebook. The significance levels were set at 0.05.(Mckinney, 2010; Kluyver et al., 2016).

4 Results

59 children (85% males and 15% females) were followed for 18 ± 8 weeks (mean ±SD).

Baseline patient characteristics are presented in Table 1.

The average doses in the morning, noon, evening and the daily total doses were as follows: Morning dose mean—4.04 ± 1.71 drops body weight; Noon mean—2.02 ± 2.28; Evening mean—3.03 ± 1.84 and Total day—7.88 ± 4.24 drops body weight (amount and timing of doses during each day was tailored to individual needs of the child, as mentioned above (e.g., higher dose at night if needed for sleep support)).

4.1 Biochemical analysis

No clinical or statistically significant differences were found in any of the analytes between baseline and at 3 months follow up. No significant change was observed in complete blood count, including hemoglobin, red blood cells or leucocytes, before and after 3 months of treatment. Platelet levels were higher before treatment (1.63 ± 46.75) compared to after treatment (8.08 ± 26.68) ($p = 0.5$) however those values are all within the normal range.

No statistically significant difference was observed in urea or creatinine before or after 3 months of treatment. No statistically significant difference was observed in liver enzymes (AST, ALT, ALP), thyroid hormones, thyroid antibodies, prolactin, or other hormones (Table 2). All of these values were within normal range. LDH was significantly higher before treatment (505.36 ± 95.1 IU/l)) as compared to its level after 3 months of treatment (470.55 ± 84.22 IU/L) ($p = 0.003$). Upon further examination of thyroid function measures, it appears that TSH values were tending to decrease while FT4 tended to increase. However, the changes in both measures remained within normal ranges. FT4 was significantly higher after 3 months of treatment (15.54 ± 1.9) as compared to its level before treatment (15.07 ± 1.88) ($p = 0.03$). TSH was higher before treatment (2.34 ± 1.17) as compared to the level after 3 months of treatment (2.05 ± 1.02) ($p = 0.01$).

A comparison of the group with additional medications ($n = 14$, Methylphenidate-4, Aripiprazole- 4, Melatonin—3, Risperdal 1, Roxetine-1, Seroquel-1), and those who received solely medical

TABLE 2 Blood analysis.

Test	Pre-treatment (Mean±SD)	After 3 months (Mean±SD)	*p* value
Albumin (ALB) (38–54 g/L)	46.37 ± 4.03	46.95 ± 2.37	0.35
Alkaline phosphatase (ALP) (117–390 U/L)	217.97 ± 71.04	220.79 ± 81.3	0.47
Alanine aminotransferase (ALT) (4–39 U/L)	16.22 ± 6.31	15.36 ± 6.49	0.15
Aspartate aminotransferase (AST) (5–38 U/L)	25.88 ± 6.39	24.88 ± 6.1	0.64
Cholesterol (140–200 mg/dl)	152.24 ± 28.27	125.75 ± 24.2	0.85
Creatine Kinase (CK) (10–170 U/L)	128 ± 68.36	123.47 ± 52.94	0.54
Calcium (Ca) (8.8–10.8 mg/dl)	9.74 ± 0.34	9.76 ± 0.32	0.8
Chloride (Cl) (96–106 nmol/dl)	101.24 ± 2.75	101.55 ± 2.35	0.63
Iron (Fe) (30–110 mcg/dL)	85.55 ± 41.18	83.76 ± 31.04	0.78
Glucose (Glu) (60–100 mg/dl)	88.93 ± 19.05	88.92 ± 16.56	1
Potassium (K) (3.10–5.10 nmol/L)	4.41 ± 0.3	4.43 ± 0.36	0.73
Lactate dehydrogenase (LDH) (240–600 U/L)	505.36 ± 95.1	470.55 ± 84.22	0.003
Sodium (Na) (135–145 nmol/L)	139.46 ± 1.99	139 ± 2.04	0.16
Prolactin (PRL) 4–15.2 (male) 4.8–23.3 (female) µl/L	9.72 ± 8.25	9.72 ± 7.95	0.99
Total protein (PROT-T) (60–80 g/L)	70.82 ± 3.47	70.79 ± 3.13	0.95
Triglycerides (TG) (30–130 mg/dl)	96.27 ± 53.77	94.96 ± 67.79	0.89
Transferrin (TRF) (2–3.6 g/L)	2.83 ± 0.59	2.85 ± 0.41	0.87
Transferrin saturation (TRFsat) (%)	22.85 ± 10.37	22.49 ± 8.91	0.89
Urea (20–45 mg/dl)	27.41 ± 9.9	25.98 ± 7.63	0.24
Creatinine (CR) 0.40–0.60 mg/dl	0.49 ± 0.18	0.49 ± 0.16	0.8
Free T4 (FT4) (12.5–21.5 pmol/L)	15.07 ± 1.88	15.54 ± 1.9	0.03
Thyroid stimulating hormone (TSH) (0.6–4.84 mU/L)	2.34 ± 1.17	2.05 ± 1.02	0.01
Hematocrit (HCT) (40–52%)	40.39 ± 3.06	40.36 ± 2.83	0.9
Platelets (PLT) (0.22–0.3 1000/µl)	283.89 ± 69.41	284.45 ± 70.22	0.92
White blood cells (WBC) (4–11%)	7.79 ± 2.08	7.36 ± 2.1	0.09
Hemoglobin (HGB) (13.5–17.5 g/dl)	13.61 ± 1.14	13.58 ± 1.04	0.75
Testosterone 9.4–37 (male) 0.2–3 (female) nmol/L	2.45 ± 5.11	3.31 ± 6.39	0.1

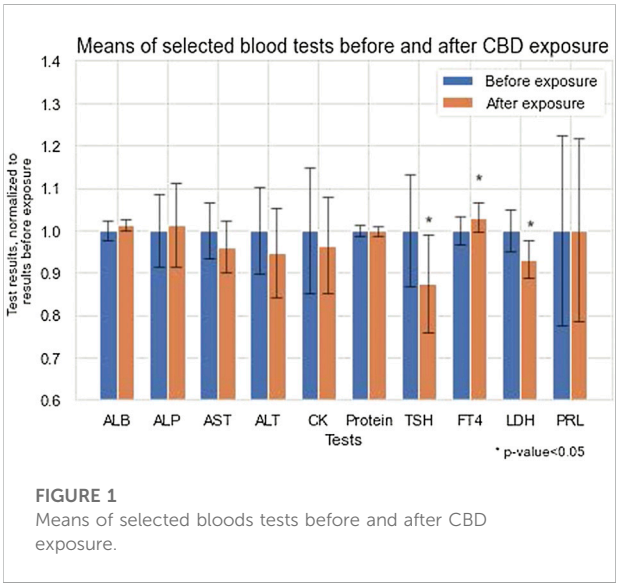

FIGURE 1
Means of selected bloods tests before and after CBD exposure.

cannabis (n = 45) showed no difference in biochemical analysis, including liver enzymes, which remained stable, except of change in potassium level, which was significantly higher before treatment (0.04 ± 0.37) as compared to after 3 months of treatment (-0.2 ± 0.33) (p = 0.04). (Supplementary Table S1). We also compared patients who received a high dose of the cannabis oil (upper quartile-16 patients receiving CBD 3.49—6.53 mg/kg body weight), with those receiving low dose (lower quartile -14 patients receiving CBD 0.7–1/- mg/kg body weight). No significant differences were observed between these two groups with regard to biochemical analysis, except of the mean change of total protein which was significantly higher among patients with high dose of CBD (0.19 ± 2.74) as compared to those with low dose of CBD (1.71 ± 2.46 (p = 0.01), and the mean change in number of platelets that was significantly lower among patients who received high dose of CBD (13.46 ± 31.38) as compared to those who received low dose of CBD (29.64 ± 26.2) (p = 0.0007) (Supplementary Table S2). The means of selected blood tests before and after CBD exposure is presented in Figure 1.

5 Discussion

This study may support the long-term safety of medical cannabis use in children and young adults with ASD. Over the first 3 months of the study, a few statistically significant changes were observed including the level of LDH and thyroid hormones, however, these changes have no clinical significance. The remaining tests which assessed hematological, chemical, and endocrine function, were all within the normal range. In addition, no differences in safety test results were identified between children taking or not taking anti-psychotic medications together with CBD-rich cannabis oil, nor between those receiving high or low dose of medical cannabis.

The recent literature presents a favorable safety profile of CBD in human trials. The majority of the available data comes from research on Epidiolex®, a 100% CBD product, in patients with epilepsy. A 2018 meta-analysis of four randomized controlled trials with patients with Lennox-Gastaut or Dravet syndrome showed that Epidiolex® was associated with a higher rate of increased serum aminotransferases compared to placebo (Lattanzi et al., 2018). Thiele et al. (2019) reported similar findings in their review of young patients with Lennox-Gastaut syndrome, treated with long-term CBD, including increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) in five and four patients, respectively (Thiele et al., 2019).

In a 2020 study on adults given 1500 mg of CBD, in the first 2–4 weeks after initiating treatment, seven (44%) participants experienced peak serum ALT values greater than the upper limit of normal. For five (31%) participants, the value exceeded five times the upper limit of normal, meeting international criteria for drug-induced liver injury (no correlation was identified between transaminase elevations and baseline characteristics, CYP2C19 genotype, or CBD plasma concentrations) (Watkins et al., 2021). Interestingly, in another trial examining the withdrawal effects of adults from CBD (20 mg/kg/day for 4 weeks), the most common adverse event was diarrhea (Taylor et al., 2020). Finally, in a study of two CBD enriched 5% oils (one with 0.25% THC 20:1, the other with 0.83% THC 6:1) on 25 patients with complex motor disorder, no changes in blood tests were found; only three patients experienced elevated CPK by the study's end and abnormalities of aminotransferase levels were found in one patient only before the study, with no changes identified during the study period (Libzon et al., 2018).

There was no effect on liver function when cannabis was given with other medications, as was reported in previous studies on Epidiolex®. A possible explanation may be that our participants received a lower dosage of phytocannaboids and the medications they received did not have the same effect as was seen with Valporal in the Epidiolex® study. Although a significant change in the TSH, FT4, and LDH was observed, they were all within normal range.

Several studies have reported on the pharmacokinetics and pharmacodynamics of cannabinoids. Two systematic reviews (Lucas et al., 2018; Millar et al., 2018) reported on the pharmacokinetics and pharmacodynamics of cannabidiol using various routes of administration, however, with paucity information in pediatric patients. In a study on healthy beagles which looked at clinical chemistry after administration of a CBD-predominant oil formulation, hematological parameters were generally normal for the dogs across these groups at 1 day and 7 days after the final dose (Vaughn et al., 2020). In their double-blind trial, Zuardi et al. investigated the effects of CBD on plasma prolactin and growth hormone among volunteers who received placebo or oral CBD at the doses of 300 mg or 600 mg; basal prolactin and growth hormone levels were unchanged after CBD (Zuardi et al., 1993).

Although our study was open-label with no placebo group, the findings support the biochemical safety of the preparation used in the study. In order to further evaluate the safety of the preparation used, a comparison was made between patients who were at the upper quartile of cannabis dosage to patients who were at the lower quartile, and no clinical significant difference was observed (Supplementary Table S2).

We also compared biochemistry analysis between patients who received other medications such as risperidone, methylphenidate, melatonin to those who received medical cannabis only (Supplementary Table S1), and the sole finding of a statistically significant change, in potassium levels between these groups, has no clinical significance.

A comparison of patients who received a high dose of the cannabis oil (upper quartile-16 patients receiving CBD 3.49—6.53 mg/kg body weight), with those receiving low dose (lower quartile—14 patients receiving CBD 0.7–1/- mg/kg body weight) showed no significant differences between these two groups with regard to biochemical analysis, except of the mean change of mean total protein, which was significantly higher among patients with high dose of CBD (0.19 ± 2.74) as compared to those with low dose of CBD (1.71 ± 2.46 (p = 0.01), and the mean change in number of platelets that was significantly lower among patients who received high dose of CBD (13.46 ± 31.38) as compared to those who received low dose of CBD (29.64 ± 26.2) (p = 0.0007) (Supplementary Table S2). However, all of these changes lack clinical significance.

It is possible, however, that due to the small number of patients receiving concomitant medications, no difference was observed.

A theoretical limitation of our study might be the open-label method, however, the biochemistry parameters examined in our study are objective numbers which are not dependent on a double-blind study.

6 Conclusion

CBD-rich cannabis oil (CBD: THC 20:1), as part of a monitored treatment program over 3 months, appears to have a good safety profile. Long-term monitoring with larger number of participants is needed. Al-Beltagi, 2021.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Author contributions

MB—Conducted research and contributed to editing and writing of manuscript AH—Conducted research and contributed to writing of manuscript EK—Conducted research and contributed to writing of manuscript OS—Conducted research and contributed to writing of manuscript RV Literature review, writing of manuscript IK Contributed to editing and review of manuscript DB—Contributed to editing and review of manuscript ML—Contributed to editing and review of manuscript AD—Contributed to editing and review of manuscript NT—Contributed to editing and review of manuscript EH—Contributed to editing and review of manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.977484/full#supplementary-material

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Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy

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There has been a dramatic increase in the number of children diagnosed with autism spectrum disorders (ASD) worldwide. Recently anecdotal evidence of possible therapeutic effects of cannabis products has emerged. The aim of this study is to characterize the epidemiology of ASD patients receiving medical cannabis treatment and to describe its safety and efficacy. We analysed the data prospectively collected as part of the treatment program of 188 ASD patients treated with medical cannabis between 2015 and 2017. The treatment in majority of the patients was based on cannabis oil containing 30% CBD and 1.5% THC. Symptoms inventory, patient global assessment and side effects at 6 months were primary outcomes of interest and were assessed by structured questionnaires. After six months of treatment 82.4% of patients (155) were in active treatment and 60.0% (93) have been assessed; 28 patients (30.1%) reported a significant improvement, 50 (53.7%) moderate, 6 (6.4%) slight and 8 (8.6%) had no change in their condition. Twenty-three patients (25.2%) experienced at least one side effect; the most common was restlessness (6.6%). Cannabis in ASD patients appears to be well tolerated, safe and effective option to relieve symptoms associated with ASD.

There has been a 3-fold increase during the last 3 decades in the number of children diagnosed with autism spectrum disorders worldwide[1–5]. No specific treatments are currently available and interventions are focussing on lessening of the disruptive behaviors, training and teaching self-help skills for a greater independence[6].

Recently, CBD enriched cannabis has been shown to be beneficial for children with autism[7]. In this retrospective study on 60 children, behavioural outbreaks were improved in 61% of patients, communication problems in 47%, anxiety in 39%, stress in 33% and disruptive behaviour in 33% of the patients. The rationale for this treatment is based on the previous observations and theory that cannabidiol effects might include alleviation of psychosis, anxiety, facilitation of REM sleep and suppressing seizure activity[8]. A prospective single-case-study of Dronabinol (a THC-based drug) showed significant improvements in hyperactivity, lethargy, irritability, stereotypy and inappropriate speech at 6 month follow-up[9]. Furthermore, Dronabinol treatment of 10 adolescent patients with intellectual disability resulted in 8 patients showing improvement in the management of treatment-resistant self-injurious behaviour[10].

In 2007, The Israel Ministry of Health began providing approvals for medical cannabis, mainly for symptoms palliation. In 2014, The Ministry of Health began providing licenses for the treatment of children with epilepsy. After seeing the results of cannabis treatment on symptoms like anxiety, aggression, panic, tantrums and self-injurious behaviour, in children with epilepsy, parents of severely autistic children turned to medical cannabis for relief.

Although many with autism are being treated today with medical cannabis, there is a significant lack of knowledge regarding the safety profile and the specific symptoms that are most likely to improve under cannabis treatment. Therefore, the aim of this study was to characterize the patient population receiving medical cannabis treatment for autism and to evaluate the safety and efficacy of this therapy.

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	Total (188)
Mean age (SD)	12.9 (7.0)
Gender (male), No. (%)	154 (81.9)
Mean body mass index (SD)	29.0 (5.3)
Previous experience with cannabis (Yes), No. (%)	19 (10.1)
Comorbidities:	
Epilepsy, No. (%)	27 (14.4)
Attention Deficit Hyperactivity Disorder, No. (%)	7 (3.7)
Tourette syndrome, No. (%)	4 (2.1)
Celiac Disease, No. (%)	3 (1.6)
Anxiety Disorder, No. (%)	3 (1.6)

Table 1. Demographic and clinical characteristics of patients at intake.

		Change at six months		
	Intake prevalence Total (188)	Symptom disappeared	Improvement	No change or deterioration
Restlessness, No. (%)	170 (90.4)	1 (1.2)	71 (89.8)	7 (8.8)
Rage attacks, No. (%)	150 (79.8)	1 (1.3)	65 (89.0)	7 (9.5)
Agitation, No. (%)	148 (78.7)	1 (1.4)	57 (83.8)	10 (14.7)
Sleep problems, No. (%)	113 (60.1)	9 (19.5)	27 (58.6)	10 (21.7)
Speech Impairment, No. (%)	113 (60.1)	—	15 (30)	35 (70)
Cognitive impairment, No. (%)	91 (48.4)	—	15 (27.2)	40 (72.7)
Anxiety, No. (%)	69 (36.7)	—	24 (88.8)	3 (11.1)
Incontinence, No. (%)	51 (27.1)	2 (9.0)	7 (31.8)	13 (59.0)
Seizures, No. (%)	23 (12.2)	2 (15.3)	11 (84.6)	—
Limited Mobility, No. (%)	17 (9.0)	2 (18.1)	—	9 (81.8)
Constipation, No. (%)	15 (8.0)	1 (12.5)	6 (62.5)	2 (25)
Tics, No. (%)	15 (8.0)	1 (20.0)	4 (80.0)	—
Digestion Problems, No. (%)	14 (7.4)	1 (12.5)	5 (62.5)	2 (25.0)
Increased Appetite, No. (%)	14 (7.4)	1 (33.3)	1 (33.3)	1 (33.3)
Lack of Appetite, No. (%)	14 (7.4)	2 (40.0)	1 (20.0)	2 (40.0)
Depression, No. (%)	10 (5.3)	—	5 (100.0)	—

Table 2. Symptom prevalence and change. Symptom prevalence at intake in 188 patients assessed at intake and change at six months in patients responding to the six-month questionnaire.

Results

Patient population. During the study period, 188 ASD patients initiated the treatment. Diagnosis of ASD was established in accordance with the accepted practice in Israel; six board certified paediatric psychiatrists and neurologists were responsible for treatment of 125 patients (80.6%), the remaining 30 children were referred by 22 other physicians. Table 1 shows demographic characteristics of the patient population. The mean age was 12.9 ± 7.0 years, with 14 (7.4%) patients being younger than the age of 5, 70 patients (37.2%) between 6 to 10 years and 72 (38.2%) aged 11 to 18. Most of the patients were males (81.9%). Twenty-seven patients (14.4%) suffered from epilepsy and 7 patients (3.7%) from Attention Deficit Hyperactivity Disorder (ADHD).

At baseline parents of 188 patients reported on average of 6.3 ± 3.2 symptoms. Table 2 shows the prevalence of symptoms with most common being restlessness (90.4%), rage attacks (79.8%) and agitation 78.7%.

Cannabis products recommended to the patients were mainly oil applied under the tong (94.7%). Seven patients (3.7%) received a license to purchase oil and inflorescence and three patients (1.5%) received a license to purchase only inflorescence. Most patients consumed oil with 30% CBD and 1.5% THC, on average 79.5 ± 61.5 mg CBD and 4.0 ± 3.0 mg THC, three times a day (for a more detailed distribution of CBD/THC consumptions see Supplementary Fig. S1). Insomnia recorded in 46 patients (24.4%) was treated with an evening does of 3% THC oil with on average additional 5.0 ± 4.5 mg THC daily. All the products content was validated by HPLC (High Performance Liquid Chromatography) in each production cycle. The cannabis dose was not significantly associated with weight (r correlation coefficient $= -0.13$, $p = 0.30$), age (r correlation coefficient $= -0.10$, $p = 0.38$), or gender ($p = 0.38$).

Follow-up, one month. After one month, out of 188 patients, 8 (4.2%) stopped treatment, 1 (0.5%) switched to a different cannabis supplier, and 179 patients (94.6%) continued active treatment (Fig. 1). Of the latter group, 119 (66.4%) responded to the questionnaire with 58 patients (48.7%) reporting significant improvement, 37

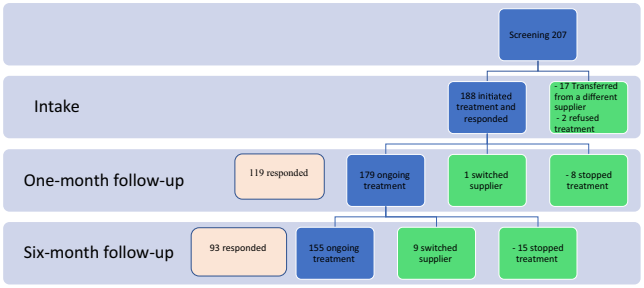

Figure 1. The study population in the three follow-up periods, at intake, after one month and after six months of medical cannabis treatment.

(31.1%) moderate improvement; 7 patients (5.9%) experienced side effects and 17 (14.3%) reported that the cannabis did not help them.

The reported side effects at one month were: sleepiness (1.6%), bad taste and smell of the oil (1.6%), restlessness (0.8%), reflux (0.8%) and lack of appetite (0.8%).

Follow-up, six months. After six months, of the 179 patients assessed in the one-month follow-up, 15 patients (8.3%) stopped treatment, 9 (4.9%) switched to a different cannabis supplier and 155 patients (86.6%) continued treatment (Fig. 1). Of the latter group, 93 (60.0%) responded to the questionnaire with 28 patients (30.1%) reporting a significant improvement, 50 patients (53.7%) moderate improvement, 6 patients (6.4%) slight improvement and 8 (8.6%) having no change in their condition. None of the variables entered to the multivariate analysis to predict treatment success was statistically significant.

To assess the potential response bias, we have compared baseline characteristics between 93 respondents and 62 non-respondents to the 6-month questionnaire. The former group was slightly older (13.7 ± 0.8 vs. 10.8 ± 0.5, $p = 0.004$).

Quality of Life. Quality of life, mood and ability to perform activities of daily living were assessed before the treatment and at six months. Good quality of life was reported by 31.3% of patients prior to treatment initiation while at 6 months good quality of life was reported by 66.8% ($p < 0.001$, Supplementary Fig. S2). Positive mood was reported by the parents on 42% before treatment and 63.5% after 6 months of treatment ($p < 0.001$). The ability to dress and shower independently was significantly improved from 26.4% reported no difficulty in these activities prior to the treatment to 42.9% at six months ($p < 0.001$). Similarly, good sleep and good concentration were reported by 3.3% and 0.0% (respectively) before the treatment and on 24.7% ($p < 0.001$) and 14.0% ($p < 0.001$) during an active treatment (Table 3).

The improved symptoms at 6 months included seizures, of the 13 patients on an active treatment at six months 11 patients (84.6%) reported disappearances of the symptoms and two patients reported improvement; restlessness and rage attacks were improved in 72 patients (91.0%) and 66 (90.3%) respectively (Table 2).

Medications Use. The most common concomitant chronic medications on the intake were antipsychotics (56.9%), antiepileptics (26.0%), hypnotics and sedatives (14.9%) and antidepressants (10.6%). Out of 93 patients responding to the follow-up questionnaire, 67 reported use of chronic medications at intake. Overall, six patients (8.9%) reported an increase in their drugs consumption, in 38 patients (56.7%) drugs consumption remained the same and 23 patients (34.3%) reported a decrease, mainly of the following families: antipsychotics, antiepileptics antidepressants and hypnotics and sedatives (Table 4). Antipsychotics, the most prevalent class of medications taken at intake (55 patients, 33.9%); at 6 months it was taken at the same dosage by 41 of them (75%), 3 patients (5.4%) decreased dosage and 11 patients (20%) stopped taking this medication (Table 4).

Side Effects. The most common side effects, reported at six months by 23 patients (25.2%, with at least one side effect) were: restlessness (6 patients, 6.6%), sleepiness (3, 3.2%), psychoactive effect (3, 3.2%), increased appetite (3, 3.2%), digestion problems (3, 3.2%), dry mouth (2, 2.2%) and lack of appetite (2, 2.2%).

Out of 23 patients who discontinued the treatment, 17 (73.9%) had responded to the follow-up questionnaire at six months. The reasons for the treatment discontinuation were: no therapeutic effect (70.6%, twelve patients) and side effects (29.4%, five patients). However, 41.2% (seven patients) of the patients who discontinued the treatment had reported on intentions to return to the treatment.

Discussion

Cannabis as a treatment for autism spectrum disorders patients appears to be well-tolerated, safe and seemingly effective option to relieve symptoms, mainly: seizures, tics, depression, restlessness and rage attacks. The compliance with the treatment regimen appears to be high with less than 15% stopping the treatment at six months follow-up. Overall, more than 80% of the parents reported at significant or moderate improvement in the child global assessment.

	Sleep			Eating with Appetite			Concentration on daily tasks			Bowel Activity		
	Before	During	p value	Before	During	p value	Before	During	p value	Before	During	p value
Severe difficulty	44 (47.3)	2 (2.2)		2 (2.2)	1 (1.1)		75 (80.6)	21 (22.6)		3 (3.2)	2 (2.2)	
Moderate difficulty	18 (19.4)	27 (29.0)		6 (6.5)	13 (14.0)		11 (11.8)	41 (44.1)		13 (14.0)	17 (18.3)	
No difficulty	28 (30.1)	39 (41.9)	<0.001	59 (63.4)	47 (50.5)	0.751	2 (2.2)	11 (11.8)	<0.001	71 (76.3)	54 (58.1)	0.242
Good	2 (2.2)	15 (16.1)		10 (10.8)	16 (17.2)		0	10 (10.8)		5 (5.4)	13 (14.0)	
Very Good	1 (1.1)	8 (8.6)		16 (17.2)	14 (15.1)		0	3 (3.2)		1 (1.1)	4 (4.3)	

Table 3. Assessment of daily activities. Ability to perform activities of daily living was assessed prior to and six months after initiation of cannabis treatment. Numbers in parenthesis represent the % of patients.

	Intake	Change at six months follow-up				
Medication family	Total	Stopped taking this medication	Dosage decreased	Has not changed	Dosage increased	New medication
Antipsychotics, n (%)	55	11 (20)	3 (5)	41 (75)	0	0
Antiepileptics, n (%)	46	6 (13)	0	35 (76)	2 (4.5)	3 (6.5)
Antidepressants, n (%)	10	3 (30)	0	4 (40)	1 (10)	2 (20)
Hypnotics and sedatives, n (%)	10	2 (20)	1 (10)	7 (70)	0	0
Anxiolytics, n (%)	7	2 (28)	0	5 (72)	0	0

Table 4. Concomitant medications. Concomitant medications use at the baseline and six months follow up in patients responding to the six-month questionnaire.

The exact mechanism of the cannabis effects in patients with ASD is not fully elucidated. Findings from ASD animal models indicate a possible dysregulation of the endocannabinoid (EC) system[11–16] signalling behaviours, a dysregulation that was suggested to be also present in ASD patients[17]. Mechanism of action for the effect of cannabis on ASD may possibly involve GABA and glutamate transmission regulation. ASD is characterized by an excitation and inhibition imbalance of GABAergic and glutamatergic signalling in different brain structures[18]. The EC system is involved in modulating imbalanced GABAergic[19] and glutamatergic transmission[20].

Other mechanism of action can be through oxytocin and vasopressin, neurotransmitters that act as important modulators of social behaviours[21]. Administration of oxytocin to patients with ASD has been shown to facilitate processing of social information, improve emotional recognition, strengthen social interactions, reduce repetitive behaviours[22] and increase eye gaze[23]. Cannabidiol was found to enhance oxytocin and vasopressin release during activities involving social interaction[16].

Two main active ingredients (THC and CBD) can have different psychoactive action mechanisms. THC was previously shown to improve symptoms characteristic to ASD patients in other treated populations. For example, patients reported lower frequency of anxiety, distress and depression[24], following THC administration, as well as improved mood and better quality of life in general[25]. In patients suffering from anxiety, THC led to improved anxiety levels compared to placebo[26] and in dementia patients, it led to reduction in nocturnal motor activity,violence[27,28] behavioural and severity of behavioural disorders[29]. Moreover, cannabis was shown to enhances interpersonal communication[30] and decrease hostile feelings within small social groups[31].

In our study we have shown that a CBD enriched treatment of ASD patients can potentially lead to an improvement of behavioural symptoms. These findings are consistent with the findings of two double-blind, placebo-controlled crossover studies demonstrating the anxiolytics properties of CBD in patients with anxiety disorder[32,33]. In one, CBD had a significant effect on increased brain activity in the right posterior cingulate cortex, which is thought to be involved in the processing of emotional information[32], and in the other, simulated public speaking test was evaluated in 24 patients with social anxiety disorder. The CBD treated group had significantly lower anxiety scores than the placebo group during simulated speech, indicating reduction in anxiety, cognitive impairment, and discomfort factors[33].

The cannabis treatment appears to be safe and side effects reported by the patients and parents were moderate and relatively easy to cope with. The most prevalent side effects reported at six months was restlessness, appearing in less than 6.6% of patients. Moreover, the compliance with the treatment was high and only less than 5% have stopped the treatment due to the side effects. We believe that the careful titration schedule especially in the ASD paediatric population is important for maintaining a low side effects rate and increase of the success rate. Furthermore, we believe that a professional instruction and detailed parents' training sessions are highly important for the increasing of effect to adverse events ratio.

The present findings should be interpreted with caution for several reasons. Firstly, this is an observational study with no control group and therefore no causality between cannabis therapy and improvement in patients' wellbeing can be established. Children of parents seeking cannabis therapy might not constitute a representative sample of the patient with the specific disease (self-selection bias). We have not formally confirmed the ASD diagnosis, however all the children included in the study were previously diagnosed with ASD by certified neurologist or psychiatrist, as required by Ministry of Health prior to the initiation of the cannabis-based treatment.

This study was based on a subjective self-report of the patient's parent's observation and not by the patients themselves. These reports, with subjective variables such as quality of life, mood, and general effects, may be

biased by the parent's opinion of the treatment. Moreover, even though the effect was assessed at six months, the possibility of the inflated expectations of the novel treatment "miracle" effect cannot be excluded. The questionnaire response rate at 6 months was 60%, thus the estimates of the efficacy and safety of the treatment can be biased. However, high compliance (above 80%) with the treatment provides a good evidence of the patients and parents satisfaction with the treatment.

While this study suggest that cannabis treatment is safe and can improve ASD symptoms and improve ASD patient's quality of life, we believe that double blind placebo-controlled trials are crucial for a better understanding of the cannabis effect on ASD patients.

Methods

Study Population. There are currently over 35,000 patients approved for medical cannabis use in Israel and 15,000 (~42.8%) of them receive treatment at Tikun-Olam Ltd. (TO), the largest national provider of medical cannabis. This study included all patients receiving cannabis license at TO with the diagnosis of autism in the years 2015–2017.

During the routine treatment process at the cannabis clinic, all willing patients underwent an extensive initial evaluation and their health status was periodically assessed by the treating team. At the intake session, the nurse assessed a complete medical history. The patient's parents were interviewed by the nurse and filled a medical questionnaire, which included the following domains: demographics, comorbidities, habits, concomitant medications, measurements of quality of life and a detailed symptoms check-list. Following intake, the nurse advised on the treatment plan.

Treatment Regiment. The treatment in majority of the patients was based on cannabis oil (an extract of a high CBD strain dissolve in olive oil in a ratio THC:CBD of 1:20, 30% CBD and 1.5% THC), and underwent an individualized titration. The starting dose was one sublingual drop three times a day with one oil drop (0.05 ml) containing 15 mg CBD and 0.75 mg Δ9-THC. Oil contained 45% olive oil, 30% CBD, 1.5% THC, <1.5% CBC, 0.5% CBG, <0.5% CBDV and <0.1% CBN. The remaining ingredients were terpenes, flavonoids, waxes and chlorophyll

In patients who reported high sensitivity to previously used medications, the treatment started with oil containing 1:20 15% CBD and 0.75% THC. In patients with severe sleep disturbances, following the initial treatment phase, 3% THC oil was added to the evening dose. In cases with a significant aggressive or violent behaviour, 3% THC oil was added.

The dose was increased gradually for each patient depending on the effect of the cannabis oil on the targeted symptoms according to the treatment plan and the tolerability of each patient. Finding of the optimal dose could take up to two months and dosage range is wide: from one drop three times a day to up to 20 drops three times a day of the same product.

After one month, the treating team contacted the parents to follow-up on the treatment progression. At six months patients underwent an additional assessment of the symptom intensity, side effects and quality of life.

Study outcomes. For safety analysis we have assessed the frequency of the following side effects at one and at six months: physiological effects – headaches, dizziness, nausea, vomiting, stomach ache, heart palpitation, drop in blood pressure, drop in sugar, sleepiness, weakness, chills, itching, red/irritated eyes, dry mouth, cough, increased appetite, blurred vision, slurred speech; cognitive side effects – restlessness, fear, psycho-active effect, hallucinations, confusion and disorientation, decreased concentration, decreased memory or other. The patient parents were asked to provide details of the incidence, duration and severity of the reported side effect.

For the efficacy analysis we used the global assessment approach where the patient parents were asked: "How would you rate the general effect of cannabis on your child condition?" the options were: significant improvement, moderate improvement, slight improvement, no change, slight deterioration, moderate deterioration and significant deterioration. Autism symptoms severity assessment included the following items: restlessness, rage attacks, agitation, speech impairment, cognitive impairment, anxiety, incontinence, depression and more. Quality of life was assessed on a Likert scale ranging from very poor to poor, neither poor nor good and good to very good[34].

The study was approved by Soroka University Medical Centre Ethics Committee and due to the nature of the data analysis based on the routinely obtained clinical data, it was determined that no informed consent is required. All methods were performed in accordance with the relevant institutional and international research guidelines and regulations.

Statistical analysis. Continuous variables with normal distribution were presented as means with standard deviation. Ordinary variables or continuous variables with non-normal distribution were presented as medians with an interquartile range (IQR). Categorical variables were presented as counts and percent of the total.

We used t-test and paired t-test for the analysis of the continuous variables with normal distribution. The non-parametric Mann-Whitney U test and paired Wilcoxon test was used whenever parametric assumptions could not be satisfied.

We utilized logistic regression for the multivariate analysis of factors associated with treatment success. We have included the following variables into the models based on clinical considerations: age, gender, number of chronic medications, number of total symptoms, and the three most prevalent symptoms: restlessness, rage attacks and agitation (as a dichotomous variable- yes/no), as reflected in the intake form.

P value < 0.05 was considered to be statistically significant. All analyses were performed at the Clinical Research Centre, Soroka University Medical Centre, Beer-Sheva, Israel using IBM SPSS version 22 (SPSS, Chicago, IL).

Declarations. The study was approved by Soroka University Medical Center Ethics Committee (study number: SCRC-0415-15) and the need for informed consent was waived due to the retrospective nature of the data analysis.

Availability of Data

The data set generated and/or analysed during the current study are not publicly available due to medical confidentiality but are available from the first author on reasonable request summarized form pending the approval of the IRB.

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Author Contributions

L.B.L.S., V.N. and R.M. planned the study; N.S. collected the data, L.B.L.S. and V.N. analysed the data, L.B.L.S. wrote the manuscript, V.N. and G.M. reviewed and approved the manuscript.

Additional Information

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January 17th 2022

Chairman Scott Lipps

Ohio House of Representatives

Health Committee

Chairman Lipps, Vice Chair Holmes, Ranking Member Russo, and members of the Ohio House Health Committee:

Thank you for letting me speak here today in regards to House Bill 60, which would allow autistic people to qualify for medical cannabis in Ohio. I have read through every comment thus far submitted to this committee in regards to this bill. I applaud the parents, doctors and advocates who have given testimony in support of this bill.

If you listen carefully, there is one voice noticeably absent from this discussion and that is the voice of an autistic person. I am here today to be that voice.

I am a 36 year old, principal software engineer with a career spanning over 15 years. I have built software that has supported the warfighter for our missions in Iraq and Afghanistan. I have designed and architected software that supports paramedics, EMTs and first responders which is used by emergency services throughout the state. I served as the chief architect and technical lead at JP Morgan Chase on their global system which automates the management and oversight for roughly 30,000 firewalls across the globe. If you bank at Chase, the software I designed is one of a handful that sits between your bank account and hackers who want your money. My work in interactive media is featured in the Kalamazoo Valley Museum, The Oklahoma Hall of Fame, the Canadian Science and Technology Museum, and Columbus's own Center of Science and Industry. In the last year, I along with hundreds of other developers helped build the software system that the U.S. Department of Health and Human Services uses to track and predict the spread of COVID-19 across the entire country.

I am also Autistic. At the age of 14, I was diagnosed with moderate-to-severe Asperger's disorder and Pervasive Development Disorder – Not Otherwise Specified (PDD-NOS). Today these two conditions are known as Autism Spectrum Disorder.

I have struggled my entire life with this. There is no cure. Like many people on the spectrum I have experienced intense physical and emotional trauma at the hands of doctors, psychiatrists, therapists, social workers, and others. I'd like to tell you some stories about how modern medicine "helped" me.

This is my story

When I was 11-13 years old I was forced to take an ungodly amount of medication. I was diagnosed by the experts with everything under the sun. At one point or another the doctors, therapists, and psychiatrists diagnosed me with Bipolar Disorder, ADHD, Oppositional Defiant Disorder, Major Depressive Disorder, and a few others I don't remember. From the ages of 8-13 I was prescribed Zoloft, Effexor, Risperdal, Paxil, Dexedrine, Lithium, Prozac, Wellbutrin, and many others I don't remember.

One thing that I do remember is waking up in the morning one day, going downstairs to my grandmother's kitchen, opening up my pill organizer which my mother prepared daily and dumping them all out in frustration on the table. I counted them. For that one day I was scheduled to take fourteen different pills. I remember that number to this day.

FOURTEEN.

I was forced to take FOURTEEN powerful, psychotropic pills EACH DAY from licensed, expert doctors with years of experience. Doctors just like those from Nationwide Children's Hospital. It broke my heart when I read the testimony of Ms. Fessel on her experiences with medicating her child. Pills and then pills to counteract the pills, and then pills to balance out those pills. Her experience mirrors my mother's. Her 10 year old's experience mirrors my own.

I ask you, does pumping a kid full of pills in this way sound like medicine to you? Because, it sounds a lot like abuse to me. It certainly felt like abuse to me when I was the 10 year old getting pumped full of pills. Of the countless pills I was fed as a child, I never once believed or felt that it helped me.

I ask, how many prescription drugs do the doctors from Nationwide Children's Hospital prescribe to the children under their care? How many pills do they stuff down the throats of the children they treat? I certainly hope that in the 22 years that have passed since I counted out fourteen pills strewn across my grandmother's kitchen table that it's a hell of a lot less today. Sadly, the testimony of Ms. Fessel indicates otherwise.

At some point during my youth, my mother could no longer afford my treatment and gave me up to the state. Eventually I ended up in foster care, where I was violently abused. I went to another family shortly after which also abused me. One day, the matriarch of my second foster care family thought it appropriate to punish me by locking me outside in the dead of winter, snow on the ground, without shoes or a coat. Her name was Joy Jackson and she is a child abuser. I don't know how many children Ms. Jackson has abused or neglected since.

The day I was locked outside is only day I genuinely tried to commit suicide, twice. First, I climbed onto I-270 and ran in front of a semi truck, which stopped just in time to save my life. Then when the police arrived I drew my wallet from my back pocket pretending it was a gun. To this day, I have no idea how I survived. I must have been unconvincing. I spent 3 months in the Franklin county juvenile detention facility for that while the state figured out what to do with me.

Eventually it was decided that I should go to an in-patient long-term-care facility called Fox Run near Chillicothe, Ohio. Upon entering the facility I was forcibly stripped of my clothes and strapped down to a hard wooden table. I could not lift my head, my feet, or my arms. I spent hours there crying in nothing but my underwear. I pissed myself on that table and laid there for at least another hour festering in my own urine.

This is how doctors and caregivers really treat autistic people. I am sure, if pressed, they will find some way to justify this. A protocol followed, a policy or rule enforced. "There was no other way", they'll say. You tell me! When is it appropriate to forcibly strip a child of their clothing and bind them to a hard wooden table? How would you justify that?

In the 3 months I spent at Fox Run I never once met with the psychiatrist in charge. I did however meet with various therapists and social workers. Eventually, it was decided that I should be removed from all of my medication as quickly as possible. Despite the risk of seizure, liver and kidney damage they stopped my medication suddenly and completely.

I spent 2 weeks twirling an unsharpened golf-sized pencil between my fingers staring at nothing at all. It felt like eternity. I think I vomited a few times along the way. I don't remember much. Withdrawal is rough. I gotta tell ya, when you take a kid with an underdeveloped brain from fourteen pills of powerful, psychotropic, anti-psychotic pills a day, down to zero it is one hell of a ride.

I am sure that the doctors from Nationwide Children's Hospital would all agree that this course of action was highly-inadvisable and dangerous. After all, I don't know of a single double-blind placebo based randomized trial that studies the effects of suddenly stopping such heroic doses of antipsychotics in children. You see, despite their objections that the "science is not yet settled" on Autism and Cannabis, doctors and clinicians often engage in dangerous treatments with limited scientific evidence or support. And that makes sense, because you cannot block every pathway to treatment simply because it is an active area of research. Every doctor, therapist, scientist, clinician, and expert makes calculated decisions based on the evidence at hand and balances it against the risks involved.

In my case, the benefits turned out to outweigh the risks. You see, after evaluating me without medication for some time, these new experts at Fox Run discovered I wasn't bi-polar after all! I didn't have ADHD, ODD, or any other condition the previous experts diagnosed me with.

It turns out I was autistic! Oh! What a discovery!

To confirm the diagnosis, I was referred to the OSU Medical Center. I underwent fMRI brain imaging and evaluation by a new panel of experts and it was agreed that I was in-fact autistic. And so my journey to recovery began!

Shortly thereafter, through various lengthy court proceedings it was determined that I would spend 6 months at Parmadale in their intensive treatment wing to undergo applied behavioral analysis with a focus on social skills development.

My 6 months there were not entirely rosy, but for the first time in my life, rather than being prescribed drugs, sedated, abused and treated like a lab rat by doctors who worship at the altar of the pharmaceutical companies, they finally sat down with me and explained to me what I was doing wrong. They answered all my questions.

Questions like:

Why do people behave like they do? Why is it so hard for me to make friends? Why did this person get offended? Why are people calling me weird all the time? When do you shake hands? How do you dress? How do you say hello? How are you supposed to look at other people? What does "what's up" mean? Why does waving your arms and rocking in your chair make people upset? Why is it bad to smile at a funeral if we're happy? Why is it that when I am honest, I make people upset?

Parmadale was far from perfect, but I attribute my recovery and success to their treatment plan and education strategy which overwhelmingly favored social skills development.

Shortly after I left Parmadale, I ended up at a public school for kids with behavioral problems here in Columbus where I was once again bullied, and abused by my peers and the adults that were supposed to be there to protect me.

A handful of months later, I decided to go live with my dad in Indiana so that I could attend a different school whereupon I promptly got myself expelled within my first year. Luckily, they let me study outside of school –

which I excelled at – and after realizing I was autistic and at the behest of my father they let me re-enroll the following year.

Two years later I graduated with honors. I went onto college where I graduated near the top of my class. I have done my best, to lead the best life I possibly can. I think I've done about as well as anyone could do. Due to my disability, I've been fired from a job on 3 separate occasions, passed over for promotions more times than I can count, and in the midst of the pandemic I was forced to vacate my apartment due to communication issues with my landlord, and which resulted in my 3rd failed relationship.

To quote one of the strongest women I know, "I'm used to it, by now".

I illustrate my ongoing struggles as an adult to dispel the myth that I am "high functioning". I am not high functioning. I struggle every single day. I often make massive mistakes, misreads, and social faux-pas due to my disability which can and do result in dire consequences. I am just lucky and fortunate enough that I have skills that are considered of high value to people without autism and which force them to deal with my quirks and issues. Most autistic people are not so lucky.

I am not high functioning. I am just skating by on luck.

I believe in my heart of hearts that caregivers, clinicians, therapists and doctors who treat people like me are overwhelmingly abusive to their patients. I think this, because I lived it. You cannot imagine the level of trauma that autistic children face at the hands of the people who are supposed to help them. Part of me hopes that maybe I just had a bad run of it; that I was unlucky. But as I've grown older and had discussions with other autistic people I have heard stories much worse than mine.

We force autistic people to behave and to communicate like non-autistic people and when we don't do what they expect, they drug us, sedate us, and lock us in rooms stripped of our clothes and our humanity. They say we don't have empathy. They are wrong.

We spend our entire lives seeking to understand the vagaries of how non-autistic people act, think and communicate. The onus to adapt and modify behavior is on us, because if we don't we are isolated, harassed, bullied, medicated, committed, and abused. We are forced to "mask and pass" using elaborate rule systems in order to maintain any acceptable standard of living and yet when you put a bunch of autistic people in the same room we communicate with each other just fine. We empathize with each other just fine. We understand each other just fine. We only struggle when we have to communicate with a person who is not autistic.

Today we know this as the "double empathy problem" and in my opinion it is the most correct theory that we have for what autism actually is. Namely, what is obvious to you isn't obvious to me and what is obvious to me is not obvious to you. Rather than celebrate this diversity in how we think we suppress everything it means to be autistic.

Non-autistic people dominate the conversation around autism. Time and time again our voices are silenced, overruled, dismissed, degraded and discarded. In the best of days our tone is policed, our approach is criticized and our words are ignored. Our doctors, caregivers, therapists, social workers, and peers continually fail to empathize with us. Despite my personal misgivings for how historically they have treated autistic people, I am a firm believer in the scientific method.

I agree with the doctors from Nationwide Children's Hospital that we need more research in this area. A lot more. We need more "gold-standard" placebo-controlled randomized trials. Still, there is a mountain of evidence piling up behind Cannabis for the treatment of autism and while these doctors look down upon us from their ivory towers, we – the autistic community – continue to suffer.

An academic review of 13 studies by Fletcher et al in August 2021 saw benefits in 61% to 93% of cases!

To quote the results of that study:

> We identified eight completed and five ongoing studies meeting the inclusion criteria. **All studies** reported substantial behaviour and symptom improvement on medicinal cannabis, with 61% to 93% of subjects showing benefit. In the three studies reporting on concomitant psychotropic medication usage and with cannabis use, **up to 80% of participants observed a reduction in concurrent medication use**.

In the testimony submitted by the doctors from Nationwide Children's hospital to the state medical board and to this committee they commented on their deep concern for the lack of double-blind, placebo-controlled randomized trials. In their letter they reference just such a study by Dr. Adi Aran and his team at Shaare Zedek Medical Center in Israel featuring 150 participants. Dr. Vandana, Patel and Newmeyer were mistaken in their belief that Dr. Aran and his team were studying the "long term effects of CBD" or that this study had yet to be completed or published.

In fact, Dr. Aran and his team published the results of this double-blind, placebo-controlled randomized trial featuring 150 participants in Feburary 2021, months before these doctors from Nationwide Children's Hospital submitted their testimony to this committee. The truth is that their study tested the effects of whole plant extract of CBD and THC at a 20:1 ratio, purified CBD and THC at the same ratio, and a placebo.

> This "gold-standard" study **was available and published long before** the doctors from Nationwide Children's Hospital submitted their erroneous report to this committee. I have the results of that trial right here.

I encourage you to read the study, but basically what this study says is that clinicians administering and monitoring the participants saw improvement of disruptive behavior in 49% of participants who were administered the whole plant extract, where the placebo control only saw improvement in 21% of participants. This is a statistically significant result (n=47; p=0.005). Additionally, the severity of the types of social impairment which is characteristic in autism (the SRS-2 is focused exclusive on autism) saw an improvement of 14.9 points (n=34) in participants who were administered the whole plant extract, where the placebo control only saw improvement by 3.6 points (n=36). This is also a statistically significant result (p=0.009).

> This study says, that when CBD **and** THC is administered to autistic children at a 20:1 ratio as whole plant extract, it reduces disruptive behaviors and decreases social impairments and that **the probability that this was not caused by any other effect, including the placebo effect is over 99.1%.**

From my own personal experience, Cannabis is a wonder-drug. I have noticed that even at low (slightly psychoactive or sub-psychoactive doses) my social impairment decreases dramatically and communicating with others becomes much more natural. With responsible use, I have seen a notable decrease in sensory overload

issues. I stim less. I get less headaches. My stomach feels better. My bowel movements are healthier. My sleep quality has improved.

I consume cannabis every single day. I rarely get “high” from it. To remain functional I engage in responsible sub-psychoactive use most of the time. I take a risk every day that I consume Cannabis. I could be arrested. I could lose my job. I could go to jail. And yet, I persist in doing it because it substantially improves my quality of life.

Opponents of medical cannabis for the treatment of autism often point to various side-effects and drawbacks, including memory loss. You know what else has these side-effects? FDA approved, expert prescribed antipsychotics and antidepressants which to this day are **still** irresponsibly and abusively over-prescribed to children. Because of these drugs, I remember very little about my life from the ages of 8-14. Most of my memories from that time are overwhelmingly traumatic. I believe that had I had access to Cannabis back then I would have much more fulfilling memories to share with you today. Sadly, they are just not there.

I hear the doctors warn of caution. It is easy to raise concerns. There will always be concerns. There will always be room for more studies. Cannabis is not without it’s side-effects. No drug is completely safe. But we now have incontrovertible scientific evidence that shows that Cannabis is an effective treatment for autism. Parents and patients should weigh the risks and benefits **with their doctors**. The doctors from Nationwide Children’s Hospital, are well within their right to advise their patients how they see fit, but I am not **their** patient.

Denying autistic people access to this life-changing, life-saving medication is morally bankrupt and inexcusable. At the end of the day, I have a right to pursue this treatment with **my** doctor.

I implore all of you to do the right thing, and pass this bill!

Thank you. I welcome any questions the committee has.

“Alone”

By Edgar Allan Poe

From childhood’s hour I have not been
As others were—I have not seen
As others saw—I could not bring
My passions from a common spring—
From the same source I have not taken
My sorrow—I could not awaken
My heart to joy at the same tone—
And all I lov’d—*I* lov’d alone—
Then—in my childhood—in the dawn
Of a most stormy life—was drawn
From ev’ry depth of good and ill
The mystery which binds me still—
From the torrent, or the fountain—
From the red cliff of the mountain—
From the sun that ’round me roll’d
In its autumn tint of gold—
From the lightning in the sky
As it pass’d me flying by—
From the thunder, and the storm—
And the cloud that took the form
(When the rest of Heaven was blue)
Of a demon in my view—

TABLE 1 Study characteristics of included completed studies

Author (date)	Sample size	% with autism	Age	Design	Length of study	Preparation; product
Aran et al. (2018) Aran et al. (2019)	57	100%	5–17.5 years	Retrospective feasibility study	7–13 months	Nonpharmaceutical standardized. Whole plant extract in olive oil, CBD:THC 20:1; given sublingually. If ineffective, lower ratios tried, up to 6:1 CBD:THC.
Barchel et al. (2019)	53	100%	4–22 years	Open-label observational study	31 to 588 days (median 66)	Nonpharmaceutical standardized. Cannabidiol oil, 30% concentration, 20:1 CBD:THC
Bar-Lev Schleider et al. (2019)	188 (93 for 6 month outcome data)	100%	Mean 12.9 ± 7 years	Prospective observational study	6 months	Unknown. Sublingual oil, 30% CBD and 1.5% THC (20:1 CBD:THC)
Fleury-Teixeira et al. (2019)	15	100%	6–17 years	Open-label observational	6–9 months	Nonpharmaceutical standardized. Cannabis extract in oral capsules; ~75:1 CBD:THC
Gaillard (2019)	1	100	5 years	Case study	2 years	Artisanal Hemp-extracted CBD with 0.005% THC; given as sublingual oil
Kruger and Christophersen (2006)	10	50%	13–16 years	Open-label prospective	6 months	Pharmaceutical. Dronabinol
Kuester et al. (2017)	21	100%	26 months to 22 years	Retrospective review	3–12 months	Unknown. Sublingual whole plant extract; ratio not controlled (72% balanced CBD:THC, 19% high CBD, 9% high THC)
Kurz and Blaas (2010)	1	100%	6 years old	Case study	6 months	Pharmaceutical. Dronabinol drops (dissolved in sesame oil)

TABLE 1 Continued

Author (date)	Daily dose	Measures	Findings	Adverse events	Discontinuation rates
Aran et al. (2018) Aran et al. (2019)	For three doses ($n = 44$): CBD: 3.8 ± 2.6 mg/kg THC: 0.29 ± 0.22 mg/kg For two doses ($n = 16$): CBD: 1.8 ± 1.6 mg/kg THC: 0.22 ± 14 mg/kg	Symptom severity and QoL scales	Considerable improvement in behaviour problems (61%), anxiety (39%), communication problems (47%). Concomitant medications: 33% received fewer or lower doses, 24% stopped entirely	Sleep disturbances (14%), restlessness (9%), nervousness (9%), loss of appetite (9%), GI symptoms (7%), unexplained laugh (7%), mood changes (5%), fatigue (5%), nocturnal enuresis (3.5%), gain of appetite (3.5%), weight loss (3.5%), weight gain (3.5%), dry mouth (3.5%), tremor (3.5%), sleepiness (2%), anxiety (2%), confusion (2%), cough (2%) Serious: Psychotic event (1 participant)	27% (3 of whom were excluded from analysis) 1—Unable to give oil 3—Side effects 5—Low efficacy 7—Low efficacy and side effects
Barchel et al. (2019)	Median dose (IQR): CBD: 90 (45–153) mg THC: 7 (4–11) mg	4 ASD comorbidity symptoms: hyperactivity, sleep, self-injury, anxiety	Overall: 75% improved, 22% no chance, 4% worsened.	Somnolence (12), appetite decrease (6), appetite increase (4), insomnia (2), abnormal response to temperature (2), eye blinking (2),	5 total (9%) 2—Low efficacy 3—Changed medical cannabis supplier or license expired

(Continues)

TABLE 1 (Continued)

Author (date)	Daily dose	Measures	Findings	Adverse events	Discontinuation rates
			Improvement by symptom: 68% hyperactivity, 68% self-injury, 71% sleep, anxiety 47%	diarrhoea (2), hair loss (1), nausea (1), confusion (1), acne (1), palpitations (1), urinary incontinence (1), eye redness (1), constipation (1)	
Bar-Lev Schleider et al. (2019)	Average dose: CBD: 79.5 ± 61.5 mg THC: 4.0 ± 3.0 mg If insomnia present: Additional 5 ± 4.5 mg THC in evening	Symptom improvement QoL, mood, ability to perform ADLs	30% significant improvement, 53% moderate improvement, 6% slight improvement, 9% no change. Statistically significant increase in QoL, positive mood, ADLs and sleep. Concomitant medication use: 34% decrease	Restlessness (6), sleepiness (3), psychoactive effect (3), increased appetite (3), digestion problem (3), dry mouth (2), lack of appetite (2)	23 total discontinued (12%); 12 due to no therapeutic effect, 5 due to side effects, 6 unknown
Fleury-Teixeira et al. (2019)	Final dose: CBD: 3.75 to 6.45 mg/kg	Symptom severity: ADHD, behaviour, motor, autonomy, communication and social interaction, cognition, sleep, seizures	93% had improvement in at least one symptom category, 47% had improvement in 4+ symptom categories Concomitant medications: 80% decreased or stopped entirely	Out of patients that completed: Sleepiness (3), irritability (2), diarrhoea (1), increased appetite (1), conjunctival hyperaemia (1), increased body temperature (1), nocturia (2). Patients that stopped: insomnia, irritability, increased HR, worsening psycho-behavioural crisis	3 stopped within 1 month due to adverse events (excluded from analysis) 1 stopped at 6 months due to worsening of psycho-behavioural crisis Total = 27%
Gaillard (2019)	60-mg CBD	Symptom severity and participation in activities	Reduced need from 1:1 support to full school without support, improved sleep, focus, attention, reduced anxiety and problem behaviours	None reported.	N/A
Kruger and Christophersen (2006)	0.14–0.36 mg/kg	Improvement, side effects	70% had significant improvement in self-injurious behaviour and overall mood	Increased appetite (2 out of 7), agitation (2 out of 10)	3 (30%); 2 due to increased agitation, 1 due to change in living situation
Kuester et al. (2017)	Not reported	Symptom severity scales	67% had significant improvements in at least one of the core symptoms of ASD	Well tolerated. More agitation (2) patients and irritability (1) resolved by changing strain	Not reported
Kurz and Blaas (2010)	3.72 mg	Symptom severity scales	Improvement in hyperactivity, lethargy, irritability, stereotypic behaviour, inappropriate speech	None reported	N/A

Molecular Autism

RESEARCH

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Cannabinoid treatment for autism: a proof-of-concept randomized trial

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Abstract

Background: Endocannabinoid dysfunction in animal models of autism spectrum disorder (ASD) and accumulating, albeit anecdotal, evidence for efficacy in humans motivated this placebo-controlled double-blind comparison of two oral cannabinoid solutions in 150 participants (age 5–21 years) with ASD.

Methods: We tested (1) BOL-DP-O-01-W, a whole-plant cannabis extract containing cannabidiol and Δ9-tetrahydrocannabinol at a 20:1 ratio and (2) BOL-DP-O-01, purified cannabidiol and Δ9-tetrahydrocannabinol at the same ratio. Participants ($N=150$) received either placebo or cannabinoids for 12-weeks (testing efficacy) followed by a 4-week washout and predetermined cross-over for another 12 weeks to further assess tolerability.

Registered primary efficacy outcome measures were improvement in behavioral problems (differences between whole-plant extract and placebo) on the Home Situation Questionnaire-ASD (HSQ-ASD) and the Clinical Global Impression-Improvement scale with disruptive behavior anchor points (CGI-I). Secondary measures were Social Responsiveness Scale (SRS-2) and Autism Parenting Stress Index (APSI).

Results: Changes in Total Scores of HSQ-ASD (primary-outcome) and APSI (secondary-outcome) did not differ among groups. Disruptive behavior on the CGI-I (co-primary outcome) was either much or very much improved in 49% on whole-plant extract ($n=45$) versus 21% on placebo ($n=47$; $p=0.005$). Median SRS Total Score (secondary-outcome) improved by 14.9 on whole-plant extract ($n=34$) versus 3.6 points after placebo ($n=36$); $p=0.009$). There were no treatment-related serious adverse events. Common adverse events included somnolence and decreased appetite, reported for 28% and 25% on whole-plant extract, respectively ($n=95$); 23% and 21% on pure-cannabinoids ($n=93$), and 8% and 15% on placebo ($n=94$).

Limitations

Lack of pharmacokinetic data and a wide range of ages and functional levels among participants warrant caution when interpreting the results.

Conclusions: This interventional study provides evidence that BOL-DP-O-01-W and BOL-DP-O-01, administrated for 3 months, are well tolerated. Evidence for efficacy of these interventions are mixed and insufficient. Further testing of cannabinoids in ASD is recommended.

Trial registration ClinicalTrials.gov: NCT02956226. Registered 06 November 2016, https://clinicaltrials.gov/ct2/show/NCT02956226

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Keywords: Autism spectrum disorder, Cannabinoids, Cannabidiol, Tetrahydrocannabinol, Clinical trials randomized controlled, Neuropsychology, Behavior, Child psychiatry, Developmental disorders, Entourage effect

Background

There is no established pharmacological treatment for the core symptoms of autism spectrum disorder (ASD), persistent deficits in social communication, and repetitive, restrictive patterns of behavior [1]; the efficacy and tolerability of pharmacotherapies addressing comorbid disruptive behaviors are relatively low [2].

Consumption of cannabis is reported to enhance interpersonal communication [3] and decrease hostile feelings [4]. The main components of the cannabis plant (phytocannabinoids) are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC activates the type-1 cannabinoid receptor (CB_1R) in the brain; it is psychoactive and can lead to anxiety and psychosis [5]. CBD, on the other hand, is an allosteric modulator of the CB_1R and might decrease the effects of CB_1R agonists such as THC. It is not psychoactive and has a relatively high toxicity threshold [5]. While THC consumption, especially at a young age, can lead to addiction, cognitive decline, motivational loss, and psychosis, co-consumption of CBD might reduce these risks [6].

CBD also appears to have anxiolytic, antipsychotic, antiepileptic, and neuroprotective properties that may be mediated through receptors such as serotonin $5\text{-}HT_{1A}$, glycine α3 and α1, TRPV1, GPR55, $GABA_A$, and PPARγ, and by inhibiting adenosine reuptake [7–11]. A single oral administration of 600 mg CBD to 34 men (17 neurotypicals and 17 with ASD) increased prefrontal GABA activity in neurotypicals and decreased GABA activity in those with ASD [12].

Epidiolex is a cannabis-derived pure CBD compound which was approved by the U.S. FDA in 2018 for the treatment of two severe forms of epilepsy [13]. This may be relevant for patients with ASD, as 10–30% also have epilepsy, and several pathophysiological pathways are implicated in both disorders [11, 14].

The endocannabinoid system is a cell-signaling system composed of the cannabinoid receptors, their endogenous ligands *(endocannabinoids, mainly* anandamide and 2-AG), transporters, and enzymes which produce and degrade the endocannabinoids [15].

Studies in animal models suggest a reduced endocannabinoid tone in ASD [16–19]. Stimulation of the endocannabinoid system [16–19] and administration of CBD [17] have improved social deficits in some models. Additionally, children with ASD have been found to have lower peripheral endocannabinoid levels [20, 21].

These preclinical data and case-series, reporting treatment with artisanal CBD-rich, cannabis strains [22–26] have triggered widespread use of various cannabis strains in children with ASD, despite a lack of controlled studies. Furthermore, the cannabis plant contains a wide range of minor cannabinoids, terpenes, and flavonoids which differ by strain. These components have also been reported to impact human behaviour [27, 28]. Various combinations of these components have been proposed to have a synergistic pharmacological effect ('the entourage effect') [29]. Whether presumed effects of cannabis in ASD should be attributed to CBD or THC, or whether minor cannabinoids, terpenes, and flavonoids also contribute therapeutically remains unclear. Accordingly, we performed a proof-of-concept, placebo-controlled trial of whole-plant extract and pure cannabinoids in children and adolescents with ASD. We hypothesized that whole-plant extract, per the entourage effect, would be more effective than placebo for disruptive behaviors; assessing this hypothesis was our primary objective. A secondary objective was to assess the efficacy of pure cannabinoids which are more standardized and repeatable than whole-plant extracts and hence more suitable for pharmacotherapy.

Methods

Standard protocol approvals, registrations, and patient consents

NCT02956226 was approved by the Institutional Review Board at Shaare Zedek Medical Center and the Israeli Ministry of Health prior to participant enrollment. Participants' parents provided written informed consent and written assent was obtained from participants when appropriate.

Study design

This proof-of-concept, randomized, double-blind, placebo-controlled trial was conducted in a single referral center—Shaare Zedek Medical Center, Jerusalem, Israel. Eligible participants were children and adolescents (5–21 years old) with an ASD diagnosis per DSM-5 criteria, confirmed by Autism Diagnostic Observation Schedule (ADOS-2), and moderate or greater behavioral problems (rating ≥ 4) on the Clinical Global Impression (CGI)-Severity scale (Table 1). Anchoring instructions (provided in the Additional file 1) were used so that the CGI-S would quantify behavioral difficulties rather than overall ASD severity.

Table 1 Inclusion and exclusion criteria for study participation

Inclusion criteria	1. Male or female outpatients aged 5–21 years old[a] 2. Diagnosis of ASD according to Diagnostic and Statistical Manual of Mental Disorders [Fifth Edition; DSM-5] 3. Moderate or greater behavioral problems as measured by a Clinical Global Impression Scale—Severity (CGI-S) score of 4 or higher at screening[b] 4. Involvement of a parent or caregiver able to consistently complete assessments throughout the study
Exclusion criteria	1. Lifetime history of psychotic disorder 2. Current or former treatment with cannabinoids 3. A medical condition (such as heart, liver, renal or hematological disorder) that impacts the subject's ability to participate in the study or makes the subject predisposed to severe adverse events 4. Subjects who have had changes in pharmacological, educational, or behavioral treatments for 4 weeks prior to randomization or planned changes in existing interventions for the duration of the trial

[a] In Israel, special education programs for individuals with ASD and neuropediatric clinics continue to follow patients with ASD until they are 21 years old

[b] To assign CGI-S scores, structured criteria were used to rate behavioral difficulties on the CGI-S, rather than overall ASD severity

Participants were randomly assigned (1:1:1 ratio) to 1 of 3 treatments for 12-weeks. Treatments were: (1) oral placebo, (2) whole-plant cannabis extract containing CBD and THC at a 20:1 ratio, and (3) pure CBD and pure THC at the same ratio and concentration. Randomization and blinding processes are described in the Additional file 1.

The primary objective was to evaluate whether whole-plant cannabis extract would induce a significant improvement in behavioral assessments compared to placebo. We used the same CBD: THC ratio as in previous open-label case series [22–24]. We did not use a 'CBD only' arm in this initial study, as we hypothesized that the CBD-THC combination would be more efficacious because of direct effects of THC on the endocannabinoid system.

For ethical reasons, we used a crossover design in which all participants would receive cannabinoids at least once: after 12-weeks of treatment ('Period-1') and a 4-week washout period, participants crossed-over to a predetermined second 12-week treatment ('Period-2'; Fig. 1). The cross-over design was intended to allow within-participant analyses, comparing the two treatments that each participant received. As we had noted a substantial improvement in our open observational study with whole-plant extract [22], we ordered treatments a priori to minimize the likelihood of substantial improvement of severe disruptive behaviors in the first period

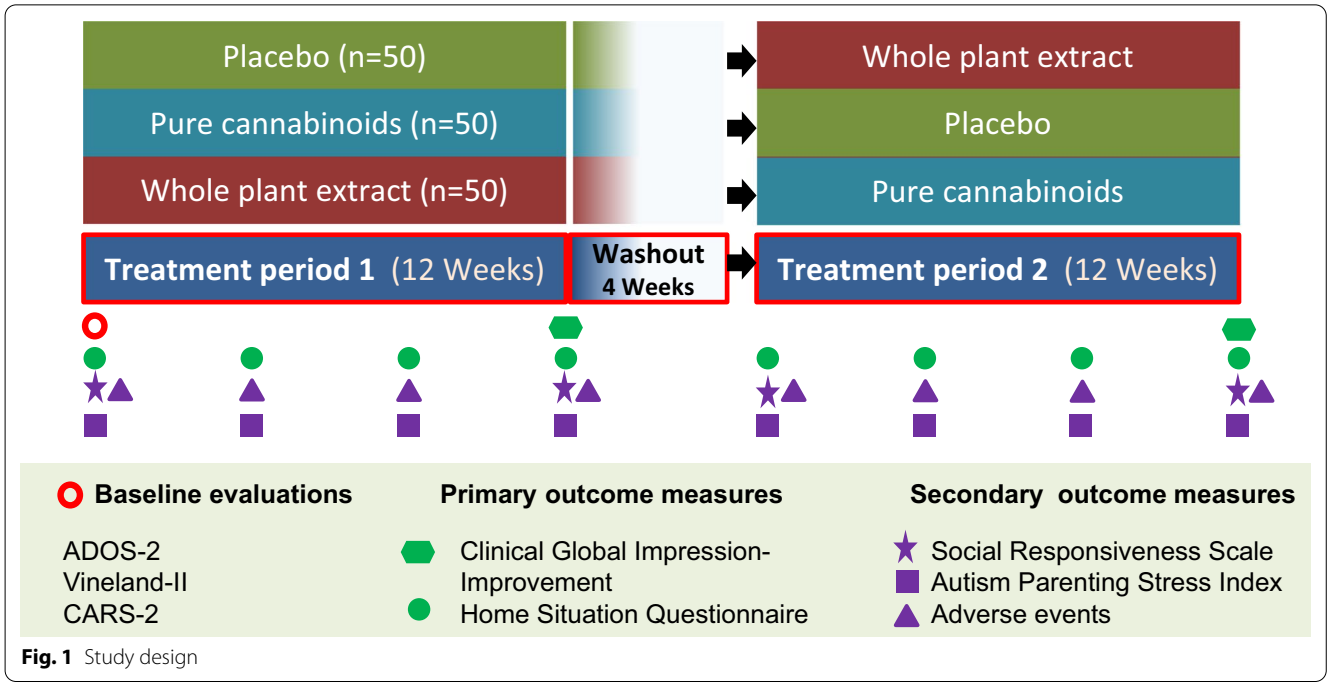

Fig. 1 Study design

and deterioration in the second period. As we hypothesized that whole-plant extract would be more effective than pure cannabinoids, we excluded the sequence of whole-plant extract followed by placebo.

Preliminary analyses revealed a treatment order effect: change from baseline was greater in the first period than in the second, suggesting a greater initial placebo effect. As a treatment order effect impairs the validity of within-participant analyses, we decided to evaluate between-group efficacy only during the first period. Data from both periods were examined for safety and tolerability. For transparency, we present within-participant analyses and between-participant analyses of period-2 (Additional file 1).

Intervention

Cannabis plants (Topaz strain; BOL Pharma, Israel) were subjected to CO_2 extraction. The extract was either immediately dissolved in olive oil (BOL-DP-O-01-W) or underwent further purification to 99% pure CBD and then was dissolved in olive oil (BOL-DP-O-01). The final concentrations of CBD and THC in both solutions were 167 mg/ml CBD and 8.35 mg/ml THC. Flavorings were added to all three solutions to make taste and scent uniform.

In each treatment period, starting dose was 1 mg/kg/d CBD (and 0.05 mg/kg/d THC). The dose was increased by 1 mg/kg/d CBD (and 0.05 mg/kg/d THC) every other day up to 10 mg/kg body weight per day CBD (and 0.5 mg/kg/d THC) for children weighing 20–40 kg or 7.5 mg/kg/d CBD (and 0.375 mg/kg/d THC) for weight > 40 kg (to a maximum of 420 mg CBD and 21 mg THC per day) divided into 3 daily doses. Treatments were given orally (sublingual whenever possible) as an add-on to any ongoing stable medication. At the end of each treatment period, the study treatment was gradually decreased over 2 weeks.

Baseline evaluations

Baseline assessments included: ADOS-2 [30], a standardized assessment of communication, social interaction, play, and imaginary use of materials; Vineland Adaptive Behavior Scales (VABS) [31], a caregiver interview assessing Communication, Socialization, and Daily Living Skills; and Childhood Autism Rating Scale-Second edition (CARS2-ST) [32], a quantitative measure of direct behavior observation.

Outcomes

Primary outcomes: We designated two co-primary outcome measures to assess ASD associated disruptive behaviors: Home Situations Questionnaire-ASD (HSQ-ASD) and CGI-Improvement (CGI-I) targeting behavioral problems.

HSQ-ASD [33] is a 24-item parent-rated measure of noncompliant behavior in children with ASD. The scale yields per-item mean scores of 0 to 9 (higher is worse) [33].

CGI-I [34] was used to measure improvement in disruptive behaviors from baseline by incorporating anchoring instructions related to behavioral difficulties (Anchors appear in the Additional file 1). As in the standard CGI-I, scores ranged from 1 (very much improved) through 4 (unchanged) to 7 (very much worse). Scores of 1 or 2 (much improved) were defined as a positive response; all others indicated a negative response [34]. CGI-I was assessed at the end of each treatment period. The same clinician (AA) assessed and rated the CGI-S and CGI-I of all participants.

Secondary outcomes included the Social Responsiveness Scale-2nd edition (SRS-2), the Autism Parenting Stress Index (APSI), and adverse events.

SRS-2: [35] this 65-item, caregiver questionnaire quantifies autism symptom severity (total scores range from 0 to 195; higher is worse).

APSI: [36] this 13-item parent-rated measure assesses parenting stress in three categories: core social disability, difficult-to-manage behavior, and physical issues.

Adverse events were assessed using a modified Liverpool Adverse Events Profile (LAEP) including the 19 original LAEP [37] items plus 15 items covering all significant adverse effects of CBD and THC reported in prior pediatric studies.

Statistical analyses

The primary aim of this study was to test the superiority of whole-plant-extract over placebo in treating ASD associated behavioral problems, using the HSQ-ASD and the CGI-I for disruptive behaviors. The comparison between pure-cannabinoids and placebo was registered as a secondary outcome. Sample size calculation was based on an effect size of $f = 0.67$ (in total HSQ-ASD score) [38] and standard deviation of 3 points in the within-participant difference between placebo and whole-plant extract conditions. To achieve 80% power with 2.5% alpha (adjusted for two co-primary endpoints) requires a sample of 43 patients per group. To account for attrition, an additional 15% were enrolled. A total of 50 participants per arm was set to test primary study endpoints. Analyses were performed using JMP version 14 (SAS Institute, Cary, NC, USA). All P values were two-sided. Specific statistical tests used and corrections applied for multiple comparisons are indicated in figure/table legends.

For details on the cannabinoid preparations, randomization process, important changes to methods after

trial commencement, anchoring instructions for rating the CGI-S and CGI-I, and the CONSORT checklist, see Additional file 2.

Results

Between 11 January 2017 and 12 April 2018, 150 children and adolescents (mean age 11.8 ± 4.1 years, median 11.25, range 5.1–20.8; 80% boys) entered the trial. ASD symptoms were 'severe' in 78.7% per ADOS-2 (Comparison Score = 8–10) [30] and adaptive level was 'low' (Standard Score ≤ 70) in 88% per Vineland Behavior Scales [31].

Screening, randomization and attrition are shown in Fig. 2 and participant characteristics are provided in Table 2. Fifty participants were randomly assigned to each of the 3 treatments in Period-1 and 44 per group completed the study (12% overall attrition).

Safety and tolerability of cannabinoid treatment with BOL-DP-O-01-W (whole-plant extract) and BOL-DP-O-01 (pure cannabinoids)

Adverse events (AEs) were reported whenever they occurred, and caregivers were proactively asked about them at each study visit, and every 4 weeks using a structured questionnaire. AEs were documented whether considered related to study treatments or not. Reports of new adverse events or worsening of previously reported events were rated mild (present, but not problematic), moderate (problematic and leading to study drug dose decrease), or severe (posing a problem requiring medical intervention). Serious AEs were possibly life-threatening events or any requiring hospitalization. Overall, 95 participants received a whole-plant extract, 93 received pure cannabinoids, and 94 received a placebo.

There were no treatment-related severe or serious AEs. Six participants had an unrelated serious event (Additional file 1: Table S1). Overall, mild AEs were not significantly more frequent during cannabinoid treatment (mild AEs were reported 383, 388, and 353 times, in 89, 79, and 78 participants during treatment with whole-plant extract, pure cannabinoids, and placebo, respectively). Moderate AEs were reported 80, 78, and 57 times, in 44, 45, and 26 participants during treatment with whole-plant extract, pure cannabinoids, and placebo, respectively. AEs that were more common during cannabinoid treatment are presented in Table 3. The full list of adverse events and correlations with age, sex, treatment dose, and concomitant medications appears in Additional file 1: Table S2.

Impact of cannabinoid treatment with BOL-DP-O-01-W (whole-plant extract) and BOL-DP-O-01 (pure cannabinoids) on behavior

The impact of cannabinoid treatment on behavioral problems was assessed using the HSQ-ASD [33], and the CGI-I [34] (co-primary outcome measures). The APSI

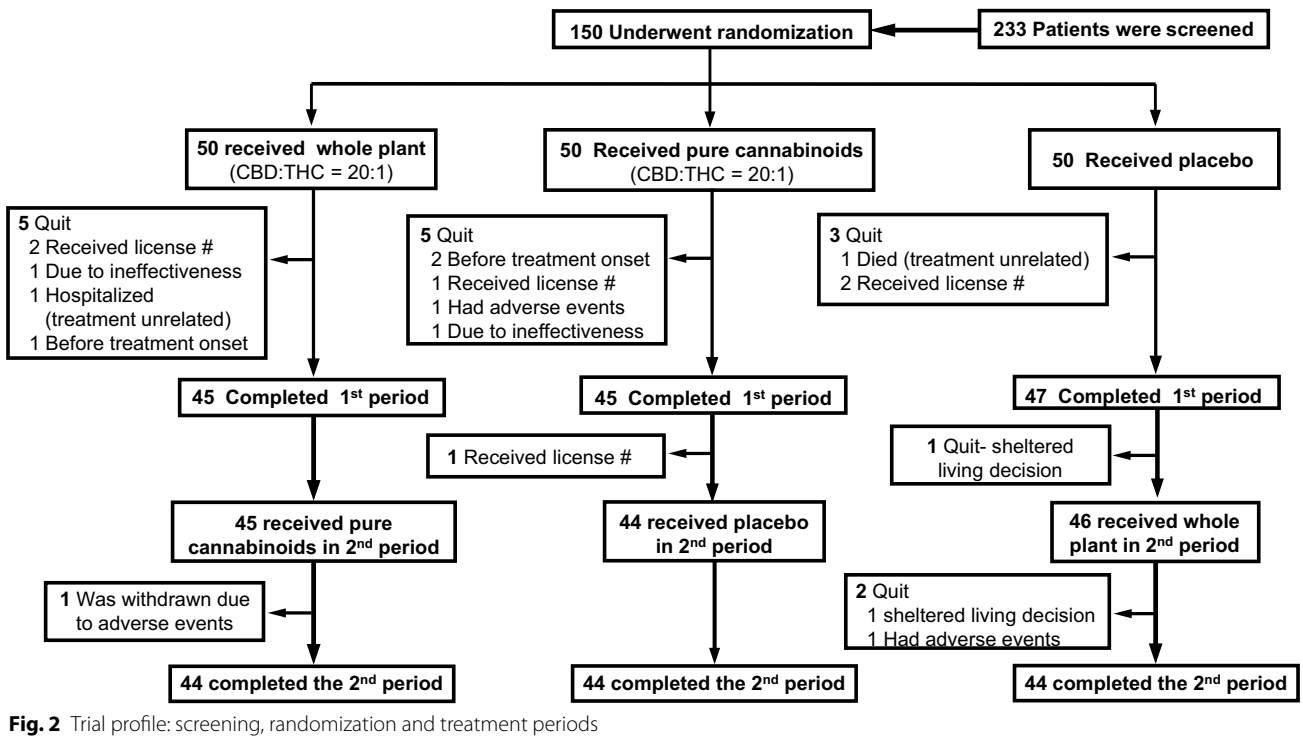

Fig. 2 Trial profile: screening, randomization and treatment periods

Table 2 Participant characteristics

	All	Placebo in 1st period; whole- plant in the 2nd	Pure cannabinoids in 1st period; placebo in the 2nd	Whole-plant in 1st period; pure cannabinoids in 2nd	*P*-value[a]
Age: mean ± SD [median, range]	11.8 ± 4.1 [11.3, 5.1–20.8]	11.7 ± 3.8 [10.7, 5.8–20]	11.6 ± 4.3 [10.3, 5.1–20.4]	12.1 ± 4.3 [12.6, 5.1–20.8]	0.79
Sex (% girls)	20%	16%	16%	28%	0.22
ADOS-2 Total Score mean ± SD [median, range]	21.8 ± 6.0 [23, 7–32]	22.1 ± 6.5 [23.5, 7–32]	22.5 ± 5.8 [24, 11–32]	20.9 ± 5.8 [21, 9–30]	0.41
VABS Standard Score mean ± SD [median, range]	52.3 ± 14.5 [51, 20–102]	52.0 ± 15.0 [49, 26–102]	52.4 ± 15.2 [54, 25–89]	52.3 ± 13.6 [52, 20–78]	0.27
CARS Total Score mean ± SD [median, range]	45.4 ± 8.4 [47.5, 29.5–59]	46.0 ± 8.5 [47.5, 30.5–59]	45.5 ± 8.9 [48.5, 29.5–57.5]	44.6 ± 7.8 [46.5, 31–56.5]	0.55
CGI-S maladaptive behavior mean ± SD [median, range]	5.6 ± 0.7 [6, 4–7]	5.5 ± 0.7 [6, 4–7]	5.6 ± 0.7 [6, 4–7]	5.6 ± 0.7 [6, 4–7]	0.78
HSQ Total Score (baseline) mean ± SD [median, range]	3.5 ± 1.7 [3.3, 0.3–8.5]	3.7 ± 1.5 [3.7, 0.7–6.0]	3.2 ± 1.5 [3.1, 0.7–6.6]	3.7 ± 2.1 [3.6, 0.3–8.5]	0.33
SRS-2 Total Score (baseline) mean ± SD [median, range]	119 ± 27 [121, 53–180]	122 ± 23 [124, 53–159]	118 ± 31 [118, 64–178]	117 ± 27 [117, 66–180]	0.37
APSI Total Score (baseline) mean ± SD [median, range]	27.1 ± 10.4 [26, 7–54]	28.3 ± 10.3 [27, 11–50]	25.8 ± 10.4 [25, 8–54]	27.4 ± 10.7 [25, 7–48]	0.67
BMI (baseline) mean ± SD [median, range]	20.8 ± 5.7 [19.0, 12.3–39.6]	20.5 ± 5.2 [19.1, 12.8–34]	20.5 ± 6.0 [19.1, 12.3–39.6]	21.3 ± 6.1 [19.0, 13.9–39.6]	0.67
Epilepsy	9%	8%	8%	10%	0.92
Concomitant medications					
Any medication	72%	72%	68%	76%	0.67
Antipsychotics	54%	58%	44%	60%	0.22
SSRIs	15%	12%	16%	16%	0.80
Antiepileptics (also given as mood stabilizers)	12%	12%	12%	12%	1.0
Stimulants	12%	8%	22%	6%	0.033
Benzodiazepines	7%	2%	8%	10%	0.19
Alpha-2 agonists	4%	4%	2%	6%	0.58

ADOS-2 Autism Diagnostic Observation Schedule-2nd edition, (Modules 1, 2 and 3 were used for 55%, 17%, and 28% of the participants, respectively, without significant differences among the 3 study arms); *VABS* Vineland Adaptive Behavior Scales; *CARS* Childhood Autism Rating Scale; *CGI-S* Clinical Global Impression–Severity [5 = markedly ill, 6 = severely ill, 7 = among the most extremely ill patients; all referencing disruptive behaviors]; *HSQ* Home Situations Questionnaire; *SRS-2* Social Responsiveness Scale-2nd edition; *APSI* Autism Parenting Stress Index; *SSRIs* Selective serotonin reuptake inhibitors

[a] Categorical parameters (sex, epilepsy and medications) were compared using likelihood ratio chi-square tests. Continuous parameters were compared using the Kruskal–Wallis test if data distribution was non-normal but similar across groups (BMI) and using median tests if data distribution was non-normal and different across groups (age, assessment scores)

[36] (secondary outcome measure) also reflects the child's behavior. HSQ-ASD total scores and APSI total scores did not differ significantly between participants who received cannabinoids and participants who received placebo (Table 4). On the CGI-I, 49% of 45 participants who received whole-plant cannabinoids responded (either much or very much improved) [34] compared with 21% of 47 on placebo ($p = 0.005$, Fig. 3). Of the 45 participants who received pure cannabinoids, 38% responded, which was not significantly higher than placebo ($p = 0.08$).

None of these 3 measures (HSQ-ASD, CGI-I and APSI) differed significantly between participants who received whole-plant extract versus pure cannabinoids (Table 4).

Second treatment period results are presented in Additional file 1: Table S3 and Additional file 1: Figure S2 for transparency but not further discussed because of a significant order effect.

Impact of BOL-DP-O-01-W (whole-plant extract) and BOL-DP-O-01 (pure cannabinoids) on Social Responsiveness Scale scores

ASD symptoms (secondary outcome) were assessed with the SRS-2 [35]. Improvement in SRS-2 total score was significantly higher following treatment with whole-plant extract compared with placebo (Table 4). Median total score improved by 3.6 points after placebo ($n = 36$) versus 14.9 on whole-plant extract ($n = 34$; $p = 0.009$) and 8.2 on pure cannabinoids ($n = 28$; $p = 0.80$). Results of the second treatment period are presented in Additional file 1: Table S3 and Additional file 1: Figure S3 for transparency.

Table 3 Common adverse events reported during either 12-week treatment period

	Whole-plant extract CBD 5.5 mg/kg/d; n = 95 (%)	Pure cannabinoids CBD 5.5 mg/kg/d; n = 93 (%)	Placebo n = 94 (%)	*P* value (placebo vs cannabinoids)
Somnolence	**27**	**24**	**7.5**	**< 0.001**
Mild	20	18.5	7.5	
Moderate	7	5.5	0	
Severe	0	0	0	
Decreased appetite	**24**	**22**	**15**	**0.157**
Mild	21	16.5	13	
Moderate	3	5.5	2	
Severe	0	0	0	
Weight loss	**12**	**13**	**4**	**0.053**
Mild	9	12	3	
Moderate	3	1	1	
Severe	0	0	0	
Tiredness	**25**	**34**	**19**	**0.077**
Mild	21	28.5	18	
Moderate	4	5.5	1	
Severe	0	0	0	
Euphoria	**20**	**19**	**13**	**0.201**
Mild	15	16	12	
Moderate	5	3	1	
Severe	0	0	0	
Anxiety	**20**	**27**	**14**	**0.084**
Mild	17	25	11	
Moderate	3	2	3	

CBD: cannabidiol (CBD:THC ratio was 20:1 for both cannabinoids tested; the average daily dose per kg was lower than the target dose as many participants weighted over 42 kg and reached the maximal daily dose)

Bold: sum of mild + moderate + severe for each adverse event

Table 4 Impact of cannabinoid treatment, as reflected by change from baseline to end of treatment period 1 in total scores of HSQ-ASD, SRS-2, and APSI

	Median (range) [*n*]			Pairwise P		
Assessment	Whole-plant extract	Pure cannabinoids	Placebo	Whole-plant versus placebo	Pure C. versus placebo	Whole-plant versus pure C
HSQ-ASD	− 1.1 (− 3.8 to 1.6) [40]	− 0.7 (− 4.4 to 3.8) [42]	− 0.5 (− 3.7 to 2.5) [39]	0.575	0.915	0.508
SRS-2	− 14.9 (− 45 to 15) [34]	− 8.2 (− 69 to 45) [28]	− 3.6 (− 63 to 35) [36]	**0.009**	0.801	0.202
APSI	− 5.4 (− 39 to 13) [38]	− 4.9 (− 19 to 22) [42]	− 1.5 (− 26 to 20) [42]	0.502	0.513	0.991

HSQ Home Situations Questionnaire–ASD; *SRS-2* Social Responsiveness Scale-2nd edition; *APSI* Autism Parenting Stress Index

Median tests were used, as distributions were non-normal

P-values are based on Mood's Median Test of each pairwise comparison

Exploratory analyses: impact of BOL-DP-O-01-W (whole-plant extract) and BOL-DP-O-01 (pure cannabinoids) treatment on Body Mass Index (BMI)

Baseline BMIs were equivalent across treatment groups (Table 2). The BMI of participants who received cannabinoids decreased during active treatment [Median {25%, 75%}] by − 0.45 {− 1.15, 0.18} in Period-1 ($n = 44$) and − 0.12 {− 0.77, 0.18} in Period-2 ($n = 40$)] following treatment with whole-plant extract; BMI decreased by − 0.36 {− 1.09, 0.24} in Period-1 ($n = 44$) and − 0.01 {− 0.61, 0.48} in Period-2 ($n = 43$) following treatment with pure cannabinoids. Changes in BMI following cannabinoid treatment (either whole-plant extract or pure cannabinoids) were − 0.36 {− 1.14, 0.2} in Period-1

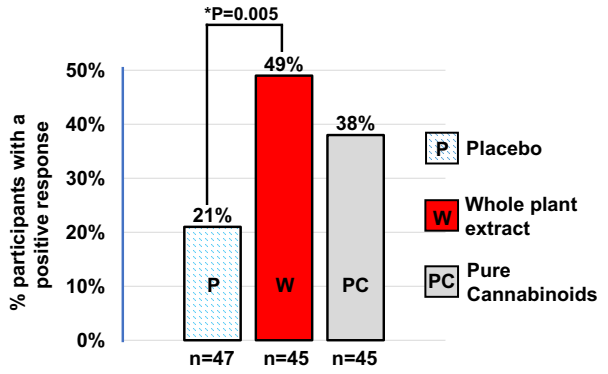

Fig. 3 Participants (%) whose behavioral problems either much improved or very much improved on the CGI-I scale following treatment. Response to 12-week treatment using the Clinical Global Impression-Improvement (CGI-I). Positive response in this scale is defined as a rating of 'much improved' or 'very much improved' [34]. Outcome was analyzed using Likelihood ratio chi-square test. *P* value is unadjusted. *Remains significant after Bonferroni-correction for multiple comparisons

($n=88$) and −0.01 {−0.7, 0.38} in Period-2 ($n=83$). During treatment with placebo, changes in BMI were 0.16 {−0.25, 0.56} in Period-1 ($n=43$; $p<0.0001$ versus cannabinoids) and 0.30, {0, 0.96} in Period-2 ($n=43$; $p=0.002$ versus cannabinoids).

Notably, participants with higher BMI at baseline had a more prominent decrease in BMI following cannabinoid treatment [The decrease in BMI was positively correlated with baseline BMI (F = 4.3, $p=0.042$ in Period-1, F = 8.6, $p=0.005$ in Period-2)]. Change in BMI following placebo was not significantly correlated with baseline BMI (Fig. 4).

Exploratory analyses: possible moderators of treatment effects

Additional file 1: Table S4 presents possible moderators of treatment response. Severity of ASD core symptoms at baseline (as assessed by ADOS-2) and concomitant use of medications were not significantly associated with response to either pure cannabinoids or whole-plant extract, on any assessment.

Males were more likely to improve on the HSQ-ASD and SRS-2. Younger children were more likely to improve on the CGI-I and APSI. Participants who had somnolence during cannabinoid treatment were more likely to respond per the CGI-I assessment. However, treatment with the whole-plant extract remained significantly

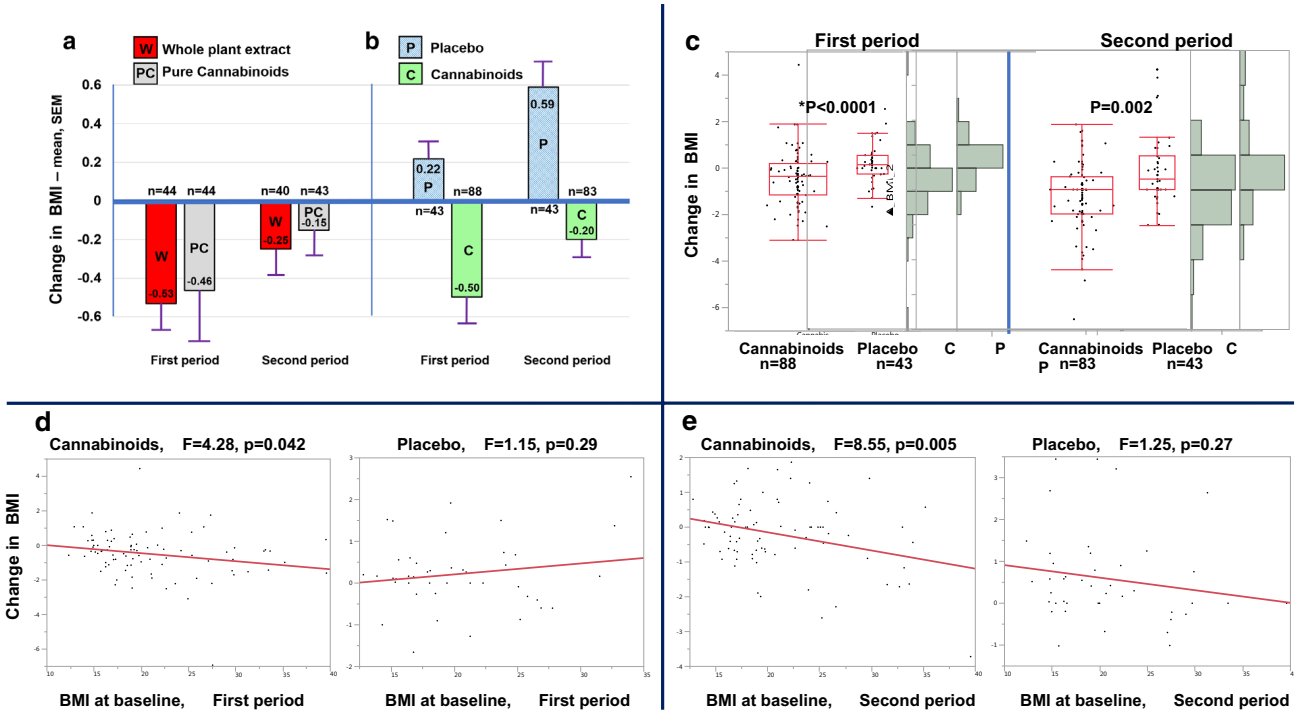

Fig. 4 Impact of cannabinoid treatment on BMI. Change in BMI during 12-week treatment with either cannabinoids or placebo. **a** Whole-plant extract versus pure cannabinoids; **b** Cannabinoid treatment (either whole-plant extract or pure cannabinoids) versus placebo; **c** Distribution of data, bars represent 10%, 25%, Median, 75% and 90%, differences between placebo and cannabinoids were analyzed using median test; **d**, **e** Change in BMI as function of baseline level, stratified by treatment (cannabinoids or placebo) and treatment period (**d** first period, **e** second period). Correlations were analyzed using linear regression

associated with improvement on the CGI-I and SRS-2 after controlling for somnolence and for concomitant use of medications during treatment [Odds Ratio {95% confidence interval} of 6.08 {1.91, 21.82} ($p=0.003$) and 3.56 {1.31, 10.28} ($p=0.015$), respectively].

Correlations between treatment dose (per Kg of body weight) and treatment response are presented in Additional file 1: Table S5. The average treatment dose during the first period was 5.7 ± 2.6 mg/kg/d of CBD in the whole-plant extract arm and 5.9 ± 2.7 mg/kg/d of CBD in the pure cannabinoids arm. A higher dose of whole-plant extract correlated with higher behavioral improvement on the CGI-I ($r_s=-0.29$, $n=45$, $p=0.050$). Cannabinoid dose did not correlate significantly with any other endpoints for either whole-plant extract or pure cannabinoids.

Concomitant medications

Study treatments were added to ongoing behavioral or pharmacological treatments. Planned changes in such treatments or a change in the 4 weeks prior to randomization were exclusionary.

Concomitant medications were taken by 72% of participants (Table 2). Adverse events or response were not significantly associated with concomitant medication use (Additional file 1: Table S2 and S3), except for somnolence which was higher in those on chronic medications ($p=0.001$).

Discussion

Currently, there are no established medications for the core autistic symptoms. Risperidone and aripiprazole have been approved by the U.S. Food and Drug Administration (FDA) to treat comorbid irritability [2] but these medications often cause obesity and metabolic syndrome [2, 39].

In this study, we have demonstrated for the first time in a placebo-controlled trial that cannabinoid treatment has the potential to decrease disruptive behaviors associated with ASD, with acceptable tolerability. This is specifically important for the many individuals with ASD who are overweight, as cannabinoid treatment was associated with net weight-loss (Fig. 4) in contrast to the substantial weight gain usually produced by antipsychotics.

Two co-primary outcomes were designated to assess improvement in disruptive behaviors following cannabinoid treatment: a parent questionnaire (HSQ-ASD) and an interview-based clinician assessment (CGI-I).

HSQ-ASD scores did not differ significantly between participants who received cannabinoids and participants who received placebo. However, as our cohort included children and adolescents with a wide range of function levels, many participants had 4 or more items which were not applicable on the HSQ-ASD, limiting sample size on this scale (Table 4).

The clinician assessment was based on a detailed description of the most bothersome behavioral problems at baseline and an extensive interview at the end of each treatment period focused on those problems. Using this patient- and family-centered tool customized for each participant, we found that 49% of participants receiving the whole-plant extract treatment responded versus 21% on placebo ($p=0.005$).

Intriguingly, one of our secondary outcomes, the SRS-2, provided preliminary evidence that cannabinoid treatment might improve core symptoms of ASD (Table 4). This finding could be of high importance if confirmed in future studies, as studies exploring pharmacological interventions for the ASD core symptoms are scarce.

Although not reportable as evidence of efficacy due to crossover effects, Additional file 1: Figures S2 and S3 show that results in the second treatment period were similar to those in the first.

Other possible implications of this preliminary study for future studies and selected clinical use include feasibility of sublingual administration in children with low adaptive level, and feasibility of a starting dose of 1 mg/kg/d of CBD and a gradual increase over 2–3 weeks to a target of 5–10 mg/kg/d divided into 2–3 daily doses.

The study explored two cannabinoid compounds, differing by the absence of terpenes, flavonoids, and minor cannabinoids in the pure-cannabinoid compound. While additive and even synergistic therapeutic effects of these additional components have been suggested ('entourage' effect) [28, 29], we did not find clear advantages for the whole-plant extract over pure cannabinoids, suggesting that attempts to search for the optimal 'entourage' effect across cannabis strains with the same CBD:THC ratio are likely to be challenging. As previously reported in studies of children with refractory epilepsy [40, 41], we also found relatively high placebo effects, emphasizing the importance of placebo in studies of medical cannabis.

Similar to these studies we also found somnolence to be the most prevalent adverse event but importantly, cannabinoid treatment remained significantly associated with a positive response on the CGI-I and SRS-2 assessments after controlling for somnolence during treatment [Odds ratio of 6.08, $p=0.003$].

Cannabinoids might affect behavior and communication through several mechanisms. THC activates CB_1R and has been associated with enhanced social behavior in multiple studies [42, 43]. CBD is a 5-HT_{1A} receptor agonist, which might facilitate anxiolytic effects. Its presumed antipsychotic effect is attributed to partial agonism at dopamine D2 receptors, similar to the antipsychotic action of aripiprazole [44].

Limitations

Our study had several limitations. Although it was designed as a cross-over study, preliminary analyses revealed a treatment order effect which prevented the use of data from the second treatment period and limited sample size. As this was the first clinical study in the ASD field, we included a wide range of levels of function. Unfortunately, the standardized questionnaires contained many items that were inapplicable for some low-functioning participants, resulting in numerous invalid scores and decreased statistical power on those measures. We did not perform genetic or intelligence quotient evaluations and could not assess the effects of genetic background or cognitive level on treatment response. We did collect data on concomitant medications but were not powered to detect effects on treatment response or on adverse events. We did not obtain data on pharmacokinetics of the interventions and concomitant medications nor tests of liver enzymes and complete blood count, although we detected no clinical evidence of hepatic or hematologic dysfunction.

Conclusions

Novel pharmacological treatments for the core and comorbid symptoms of ASD are urgently needed. Preclinical studies implicate the endocannabinoid system in the pathophysiology of ASD. In a controlled study of 150 participants, we found that BOL-DP-O-01-W, a whole-plant extract which contains CBD and THC in a 20:1 ratio, improved disruptive behaviors on one of two primary outcome measures and on a secondary outcome, an index of ASD core symptoms, with acceptable adverse events. These data suggest that cannabinoids should be further investigated in ASD.

Future studies should consider recruiting participants within narrower ranges of age and functional levels, assess the long-term tolerability and safety of cannabinoid treatments, and identify target populations within the autism spectrum that might benefit most from these treatments.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13229-021-00420-2.

Additional file 1. Data Supplement.

Additional file 2. CONSORT checklist.

Abbreviations

APSI: Autism Parenting Stress Index; ASD: Autism spectrum disorder; CB_1R: Type-1 cannabinoid receptor; CBD: Cannabidiol; CGI-S/CGI-I: Clinical Global Impression–Severity/Improvement; HSQ: Home Situations Questionnaire; SRS: Social Responsiveness Scale; THC: Tetrahydrocannabinol.

Acknowledgements

The statistical analysis was conducted by: Elliot Sprecher, PhD, Technion Faculty of Medicine, Haifa, Israel and Yishai Friedlander, M.P.H, Public Heath, Ben-Gurion University, Israel. Anchoring instructions for rating the CGI-S and CGI-I were developed in consultation with Dr. Elizabeth Berry-Kravis.

Authors' contributions

Dr. Aran conceptualized and designed the study, recruited participants, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Ms. Harel collected data, carried out the initial analyses, and reviewed and revised the manuscript. Drs. Cassuto, Schnapp, Watted, Shmueli and Golan recruited participants, collected data, and reviewed and revised the manuscript. Ms. Polyansky designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscrip. Dr. Castellanos interpreted data, drafted the initial manuscript, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Availability of data and materials

The authors declare that the data supporting study findings are available within the paper and its Additional file. The remaining data are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

All research procedures were approved by the Shaare Zedek Medical Center Review Board and Israeli Ministry of Health prior to participant enrollment. Participants' parents provided written consent prior to initiation of any experimental procedures, and written assent was obtained from participants when appropriate.

Consent for publication

Not applicable.

Competing interests

Adi Aran and F. Xavier Castellanos report receiving personal fees and stock options for advisory roles at BOL Pharma. The remaining authors have no conflicts of interest to disclose.

Author details

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5. **Letters of support provided by physicians with knowledge of the disease or condition. This may include a letter provided by the physician treating the petitioner, if applicable:**

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To Whom It May Concern,

My name is Dr. Uma Dhanabalan and I am a doctor specializing and certified as a Diplomat through the American Academy of Cannabanoid Medicine. I have recommended Medical Cannabis since 2014 and have been writing recommendations for medical marijuana (Cannabis) since 2012. My clinic is Uplifting Health and Wellness located in Cambridge, Massachusetts. Our youngest patient is 2 and our eldest is 98. I write recommendations for patients who qualify in the state of Massachusetts, Maine, New Hampshire, Vermont, Georgia, Washington, Connecticut, Rhode Island and I consult for people all over the world. I have treated and worked with patients with Autism and Autism Spectrum Disease (ASD) for years - initially as a Family Doctor. I have found Cannabis to be a much safer option and can be used as an adjunct therapy that can help reduce and eliminate other medications and improved quality of life. This impact is not only for the patient, but also for their families, caregivers and society.

Only two drugs have been approved by the FDA for autism and both are specifically approved to manage irritability associated with the disorder. Patients with autism are frequently treated with off-label drugs that were developed to treat other serious medical conditions and have been found to be somewhat effective in alleviating symptoms of ASD. Side effects of some of these drugs include rapid weight gain, seizures, increased energy, dyskinesia, decreased appetite, increased irritability, social withdrawal, restlessness and rage.

The medicines available to help the symptoms of Autistic Spectrum Disorder are not very effective, are sometimes not tolerated well and can have several undesirable side effects. Many suffering from Autism experience chronic and debilitating conditions, and Cannabis serves as a beneficial and safer alternative which has been around for thousands of years.

With the incidence of Autism diagnoses increasing over the years, specifically with adults, it's imperative that medical professionals have all the tools necessary to assist these patients, including the ability to recommend Cannabis.

Cannabis use has been reported to calm hyperactivity and decrease irritability, as well as help with sleep. It has enabled some to comply with directions and requests of family members and caretakers better facilitating tolerance of social settings without undue mental distress by decreasing irritability. Cannabis has also decreased self-harm and hostility towards others allowing them to be in less restrictive environments in the community.

For these reasons I am fully supportive of the use of alternative medicine to treat people suffering from all forms of Autism.

Should you have any questions regarding my support please feel free to contact me.

Best,

Dr. Uma Dhanabalan
MD MPH FAAFP MRO CMS

UPLIFTING HEALTH & WELLNESS
THE FUTURE OF MODERN MEDICAL PRACTICE

Dr. Uma Dhanabalan

MD MPH FAAFP MRO CMS

Dr. Uma Dhanabalan is a highly respected physician known to most as Dr. Uma. She is the Founder/CEO of Global Health & Hygiene Solutions, LLC, established in 2006, with a mission to "promote wellness and prevent illness"Ô and Uplifting Health & Wellness"Ô , an Independent Medical Practice. Dr. Uma's mission is to change the stigma regarding Cannabis and for the world to know about the Endocannabinoid system through education. She is an educator, advocate, activist and speaks locally & globally about cannabis as a plant medicine and global solution.

She created the model TotalHealthCareTHCÔ where she "Educates, Embraces and Empowers" her patients, the public, policymakers, etc. and promotes cannabis as a treatment option. She created the panel "Doc and Jocks"Ô with Dr. Uma the "Doc" and various famous athletes, the "Jocks" that are using cannabis to promote her mission and message. Dr. Uma Says® "Cannabis is not for everyone, yet it should be a first line option, not the last resort." "Cannabis is an entrance to a better quality of life, an exit drug from pharmaceuticals, narcotics, alcohol, and nicotine." "Safety first, Do No Harm." Cannabis The Exit Drug®".

She has received awards from the American College of Occupational & Environmental Medicine for her research project: "Occupational & Environmental Exposure to Lead in South India" from The 7th World Ayurveda Conference & Arogya Expo for her presentation "Cannabis & The Therapeutic Uses", The Educational Achievement Award presented by Clover Leaf at Cannabis Business Award 2017, Award from High Times Inaugural Female 50, The International Cannabis Activist Award at The 10Th Anniversary Cannabis Business Awards 2022 , Cannabis Philanthropist Award 2022-2023 "Blood, Sweat & Tears" from the Crohn's Charity Service Foundation.

She received her Bachelor of Arts with High Honors from Rutgers University. Her Medical Degree from the University of Medicine & Dentistry. She completed her Family Practice Residency at the Medical University of South Carolina, Her Master in Public Health, Occupational & Environmental Medicine Residency and Fellowship in Heavy Metals at the Harvard School of Public Health.

She is a Fellow of the American Academy of Family Physicians, a Diplomat of the American Academy of Cannabinoid Medicine as Cannabinoid Medicine Specialist and Certified by the Medical Review Officer Certification Council as a Medical Review Officer.

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EDUCATION

Fellowship
July 1999 – June 2003
Department of Environmental Health
Co-Chief Resident
Harvard School of Public Health
Boston, MA

Graduate School
August 1998 - June 1999
Masters in Public Health
Harvard School of Public Health
Boston, MA

Residency
July 1995 - June 1998
Department of Family Medicine
Medical University of South Carolina
Charleston, SC

Medical School
August 1991 - June 1995
Medical Degree
UMDNJ - New Jersey Medical School
Newark, NJ

College
August 1981 - May 1984
Bachelor of Arts
Zoology & Physiology - High Honors
Rutgers University
Newark, NJ

CERTIFICATES

Board Certified in Occupational Medicine (2005 to 2015)
Board Certified in Family Medicine (1998 to 2005)
Fellow American Academy of Family Medicine
Medical Review Officer (2003-2016, 2018-2023)
Diplomat Certified Cannabinoid Medicine Specialist 2014

AWARDS AND HONORS

Rutgers University, May 1984
Alpha Sigma Lambda Honor Society
Rutgers University, May 1984
Excellence in Science Award
American College of Occupational & Environmental Medicine, April 2000
Frontier in Occupational & Environmental Medicine Award
7th World Ayurveda Congress & Aroyga Expo December 2016
The Endocannabinoid System & Therapeutic Uses of Cannabis
5th Annual Cannabis Business Awards 2017
"Educational Achievement Award"
Harvard T.H.Chan School Of Public Health, 2019
Lighting Talk Presenter – Misinfodemic - "Cannabis The Exit Drug"
Cannabis Business Awards 10th Anniversary 2022
"International Cannabis Activist Award"

WORK EXPERIENCE

08/14 – present	Uplifting Health and Wellness, LLC Cambridge, Massachusetts Founder, CEO
06/06 – present	Global Health & Hygiene Solutions, LLC Cambridge, Massachusetts Founder, CEO
09/11 – 10/12	Medcor at Bechtel Occupational Health Services Richland, Washington Occupational Medicine Physician
05/10 –08/11	Advanced Med Hanford Occupational Health Services Richland, Washington Occupational Medicine Physician
04/09 –05/10	Caritas Physician Network Brockton, Massachusetts Family Practice/Occupational & Environmental Medicine
09/06 – 12/08	Caritas Good Samaritan Hospital Occupational Health Services Avon, Massachusetts Occupational Medicine Physician
07/05 – 03/06	Kimberly Clark Corporation – Health Services Roswell, Georgia Regional Medical Director-Roswell, Consultant, South Asia Developing & Emerging Countries
09/03 - 06/05	Kimberly Clark Corporation – Health Services Roswell, Georgia Associate Medical Director-Roswell
9/03 – 01/15	Emory University Atlanta, Georgia Preceptor for Occupational Medicine
7/02 – present	Harvard School of Public Health Boston, Massachusetts Visiting Scientist
9/99 - present	Kindred-Northeast Specialty Hospital Braintree, Massachusetts Occupational Medicine Physician
8/02 – 4/03	Quadrant Health Strategies Peabody, Massachusetts

Medical Director

12/00 - 4/02 Corporate Care St. Joseph Hospital
Occupational Health & Safety Service
Providence, Rhode Island
Medical Director

5/00 - 9/00 Polaroid Corporation
Waltham, Massachusetts
Physician, Occupational Medicine

5/00 - 9/00 Olympus Hospital
Braintree, Massachusetts
Physician, Primary Care / Intensive Care

10/00 -12/00 Occupational Health and Rehabilitation
Wellesley, Massachusetts
Physician, Occupational Medicine
"Moonlighting" – Coverage as needed for Occupational Medicine Physicians

7/98 - 9/99 MUSC- Graduate Medical Office
Charleston, South Carolina
Resident Co-Coordinator

I was involved with a pilot project that exposed residents to Care Management in Family Medicine and Internal Medicine. Prepare application for ACGME accreditation for Transitional Year program at MUSC

4/91 - 6/95 UMDNJ- Department of Obstetrics & Gynecology
Newark, New Jersey
Research Teaching Specialist

Trained and assisted Reproductive Endocrine Fellows in projects involving tissue culture of granulosa cells obtained for patients undergoing in vitro fertilization, and performed Radioimmunoassay to measure progesterone production and the effect of various inhibitors.

4/88 - 5/91 Prudential Insurance Company
Fairfield, New Jersey
Personal Injury Claims Representative

Handled claims filed by insured, who had been involved in personal injuries due to motor vehicle accidents, work injuries and other causes. It involved medical follow-ups with treating physicians and others. Knowledge of the policy's liabilities and limits.

9/85 - 9/87 Rutgers University
Newark, New Jersey
Teaching Assistant

Taught and tutored undergraduate students in general biology laboratory, anatomy and physiology laboratory.

CMDNJ - Department of Obstetrics & Gynecology, Department of Preventive Medicine
Newark, New Jersey
Research Assistant

Collected data to study the prophylaxis use of Trimethoprim Sulfamethoxazole in women undergoing cesarean section.

CMDNJ - Department of Surgery and Department of Radiology
Newark, New Jersey

Laboratory Technician

Tumor biopsy samples obtained from patients with head and neck cancer were implanted in the sub-renal capsule of mice. Various chemotherapy agents, in combination, were studied, and its effect on tumor growth and or reduction. Studies were also conducted to see the effect of coagulation in the presence of tumor and resection of tumor.

6/81- 6/82 CMDNJ - Department of Surgery
Newark, New Jersey
Volunteer - Laboratory Assistant

Designed and conducted various studies using animal models to study the effect of diabetes on microcirculation, effect of ethanol on murine burns, and frostbite.

RESEARCH ACTIVITIES

Ayyadurai UV, Spillert CB, Vidaver RM, Lazaro EJ: Assessment of diabetic microcirculation with intravital dye. Clinical Research 30(2): 169, 1982 - abstract.

Spillert CR, Murphy TV, Hollinshead MA, **Ayyadurai UV**, Lazaro EJ: Effect of ethanol on murine burns. Presented - Fifth Annual Conference on shock. June 9-11, 1982, Clinical Research 30(3): 683, 1982 - abstract.

Spillert CR, Machiedo GW, **Ayyadurai UV**, Lazaro EJ: Increased lethality of endotoxemia in murine frostbite. Presented - Fifth Annual Conference on shock. June - 11, 1982.

Raina S, Greenstein SM, **Dhanabalan UVA**: Sub-renal capsular assay. Presented at the Oncology Society of New Jersey. West Orange, NJ. December 1, 1982.

Greenstein SM, Raina S, **Ayyadurai UV**, Spillert CR: Changes in blood coagulation before and after tumor resection. Presented - New York Academy of Science, New York, NY January 1983.

Raina S, Spillert CR, Greenstein SM, **Dhanabalan UVA**, Lazaro EJ: Effect of surgery on tumor-induced accelerated coagulation in a rat squamous cell carcinoma. Presented at the Seventeenth Annual Meeting of the Association for Academic Surgery. Syracuse, NY. November 1983.

Greenstein SM, Raina S, **Ayyadurai UV**, Spillert CR: Curative surgery abolishes accelerated coagulation. Presented -Residents section at the Annual Meeting of the Society of University Surgeons. Oklahoma City, OK February 9, 1983, Current Surgery 41(3): 182-3, 1984, May-June.

Brown JR, Gagliardi CL, Saketos M, **Dhanabalan UVA**, Weiss G: Relaxin and progesterone secretion by epithelioid and fibroblastic variants of hCG stimulated luteinized human granulosa cells (LHGC) in culture Presented - American Fertility Society Forty-eighth Annual Meeting. New Orleans, LA. November 2-5, 1992.

Saketos M, Gagliardi CL, **Dhanabalan UVA**, Weiss G, Goldsmith LT: Does an autocrine effect of relaxin exist in human luteinized granulosa cells? Presented - Seventy-fifth Endocrine Society Meeting. Anaheim CA. June 15-18, 1994.