

Autism Spectrum Disorder (ASD)

ISSUE BRIEF ON AUTISM SPECTRUM DISORDER (ASD)

Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies of cannabis therapy are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Though the MN medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

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. These essential markers of autism spectrum disorder present in early childhood and limit everyday functioning. The word "spectrum" is used to define ASD since the disorder manifests itself in diverse ways, depending on varying symptom severity, the individual's development level, and chronological age (American Psychiatric Association 2013).

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is the 2013 update to the American Psychiatric Association's classification and diagnostic tool. In the U.S. the DSM serves as the primary authority for psychiatric diagnosis. In the latest version of the DSM, several disorders have now been incorporated into the ASD definition, such as Kanner's autism and Asperger's disorder, among others. 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:
 1. 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.
 2. 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.
 3. 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.
 4. (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:
 1. 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).
 2. 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).
 3. 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).
 4. 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).
 5. (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.

Prevalence

The Centers for Disease Control and Prevention estimates that 1 out of every 68 children in the United States has autism spectrum disorder. ASD is roughly 4.5 times more common among boys than girls (Christensen 2016). Since 2006, the prevalence of childhood ASD has increased by 23%, becoming a major public-health concern. This increase in prevalence can be attributed to better screening and the DSM-5's broader definition of ASD, among other issues (Harrington and Allen 2014).

Among both children and adults, roughly 3.5 million Americans live with autism spectrum disorder. Annually, costs associated with children who have ASD are \$61 billion in the United States. Adults living with ASD cost the U.S. \$196 billion per year (Buescher 2014).

Current Therapies

Several behavioral, educational, and pharmaceutical treatments are used to manage ASD. Pharmaceutical treatments mostly target comorbid health problems, which are common in children living with ASD (McPheeters 2011).

Behavioral and developmental interventions are the primary treatments for ASD (Ospina 2008). There is a great variety in the kinds of behavioral and developmental interventions, which are organized into smaller subcategories (Ospina 2008). For example, within the continuum of behavioral and developmental interventions, applied behavioral analysis (ABA) is designed to teach socially appropriate behaviors and to decrease challenging behaviors (Harrington 2014, Ospina 2008). Another kind of behavior and developmental intervention is social skills training (SST), which targets social deficits (White 2007).

ABA-based therapies have demonstrated positive effects on language, adaptive, cognitive, and educational outcomes (Hanley 2001, Lovaas 1987, Warren 2011). However, there is a lack of high-quality randomized controlled trials (Warren 2011). The studies that do evaluate behavioral and developmental interventions are methodologically weak, include few participants, and do not evaluate long-term effects of interventions (Ospina 2008). Therefore,

the evidence to determine which behavioral interventions are most effective in children with ASD is inadequate (Warren et al., 2011). Studies on SST interventions are similarly low-quality, though evidence from several small, initial studies indicate that SST is potentially beneficial to children with ASD (White 2007).

Common comorbidities in children with ASD include intellectual disability, constipation, sleep disorders, anxiety, ADHD, and seizure disorders (Harrington and Allen, 2014; McPheeters 2011). Treating comorbid mental-health issues in children with ASD is more challenging than treating common medical problems, such as constipation and sleep problems (Harrington 2014). Antipsychotic medications, serotonin-reuptake inhibitors, and stimulants are among the pharmaceuticals used to treat mental-health comorbidities (McPheeters 2011). However, despite the fact that medications are used to treat many children with ASD, there is little evidence to indicate that these pharmaceuticals are effective (McPheeters 2011). Drugs that do demonstrate benefits for challenging or repetitive behaviors, are unfortunately associated with adverse effects, limiting their use to patients with severe impairments or risk of injury (McPheeters 2011).

Turning to adolescents and young adults with ASD, studies examining the effectiveness of behavioral, pharmaceutical, and other therapies in this population are poor-quality (Taylor 2012). There is a dramatic lack of evidence on the best way to treat adolescents and young adults who have ASD (Dove 2012, Taylor 2012).

Pre-Clinical Research

A September, 2017 review by Zamberletti et al (Zamberletti 2017) provides a good overview of the lines of evidence from animal studies suggesting the endocannabinoid system (ECS) plays a role in autism. Recently, at least three articles (Doenni 2016, Servadio 2016, and Wei 2016) have reported on studies that manipulated the ECS in mouse models of autism.

Zamberletti E, Gabaglio M, Parolaro D. The endocannabinoid system and autism spectrum disorders: Insights from animals. *Int J Mol Sci* 2017;18(9). pii: E1916. doi: 10.3390/ijms18091916

This review provides evidence of involvement of the ECS in autism through modulation of autism-like behaviors and research suggesting possible mechanisms of action.

Genetic-based models:

- Fragile X syndrome (FXS) is the most common known genetic cause of ASD. A mouse model of FXS has been developed: the Fmr1 knockout mouse. Fmr1 mice have been shown to have dysregulated endocannabinoid signaling. And studies that inhibited different enzymes that degrade endocannabinoids showed improvement in autism-consistent behaviors.
- Inbreeding has produced a group of mouse strains used as a model for idiopathic (cause unknown) autism because the mice exhibit behaviors consistent with those seen in humans with ASD, but with no known gene mutation causing the behaviors. Prominent among these strains is the BTBR mouse model. Treatment to increase the level of one

endocannabinoid (AEA) resulted in reduced ASD-like behavior.

Environmental-based models – environmental manipulations in rodents conducted using the same agents that have been correlated with human autism:

- The valproic acid (VPA) rat model has been used extensively to evaluate the possible involvement of the endocannabinoid system in ASD. VPA is an anti-epileptic drug. Several studies have shown use of VPA during pregnancy may cause neural tube defects and cognitive impairment in children. In animal studies, offspring of rats administered VPA during pregnancy show lower social interaction, increased repetitive/sterotyped behaviors, early signs of neurodevelopment impairment, and abnormal responses to painful and non-painful stimuli. Studies have been done administering to rats exposed to VPA in utero substances that inhibit the breakdown of an endocannabinoid (AEA). Results showed decrease in the autism-model behaviors, with greater decrease seen in males.
- Both viral and bacterial infections during pregnancy have been linked to an increased risk to develop ASD in the offspring. Injection of pregnant rodents with the substance, polyinosine:cytosine (LPS), which mimics the immune activation seen with the influenza virus, produces ASD-like behaviors in the offspring. These include impairments in social interaction and communication, stereotyped patterns of behavior, anxiety, and impaired learning and memory. These behaviors in the offspring were accompanied by distinctive changes in brain neuron structure and function. The tie to the endocannabinoid system comes with studies that administered LPS to rodents soon after birth. This resulted in decreased social play, reduced CB1 (cannabinoid receptor 1) binding, and increased levels of the endocannabinoid, AEA.

Possible mechanisms of action:

- Studies have shown elements of the ECS interact with oxytocin, a neuropeptide that promotes parental and social bonding. Oxytocin stimulates endocannabinoid release in a relevant part of the brain (nucleus accumbens) and there is evidence endocannabinoid signaling is required for the prosocial effects of oxytocin.
- mTOR signaling is involved in memory consolidation and normalization of mTOR signaling in the hippocampus reduces the cognitive deficits caused by cannabinoid receptor 1 blockade of Fmr1 (fragile X Syndrome model) mice. Dysregulation of mTOR signaling appears to be a feature common to a subset of ASD. (mTOR is an enzyme that controls cell growth and metabolism).
- There is evidence that endocannabinoids might modulate ASD symptoms via interaction with immune system cells. Changes in endocannabinoid metabolism and in expression cannabinoid receptors (CB2) on certain white blood cells have been seen in ASD patients.

The authors conclude, “Although preclinical findings seem to suggest that pharmacological interventions aimed at modulating the EC system could be beneficial for relieving symptoms associated with ASD, their preliminary nature does not allow any definitive conclusions to be

drawn concerning potential therapeutic exploitation.”

Doenni VM, Gray JM, Song CM, Patel S, Hill MN, Pittman QJ. Deficient adolescent social behavior following early-life inflammation is ameliorated by augmentation of anandamide signaling. *Brain Behav Immun* 2016;58:237-247.

Inflammation was induced in 14-day old rats with administration of a lipopolysaccharide. Control rats received a saline injection. Subsequent differences in social behavior tests and in endocannabinoid system were studied. LPS-injected rats exhibited a lower level of social behavior. Oral administration of an inhibitor of the enzyme that degrades the endocannabinoid AEA resulted in none of the social behavior impairment expected in LPS-injected rats. Control rats were unaffected.

Servadio M, Melancia F, Manduca A, di Masi A, Schlavi S, et al. Targeting anandamide metabolism rescues core and associated autistic-like symptoms in rats prenatally exposed to valproic acid. *Transl Psychiatry* 2016;6 e902 doi:10.1038/tp.20616.182.

The following is from the article’s abstract. Anandamide is one of the primary endocannabinoids. “VPA-exposed rats showed early deficits in social communication and discrimination, compromised sociability and social play behavior, stereotypies and increased anxiety, thus providing preclinical proof of the long-lasting deleterious effects induced by prenatal VPA exposure. At the neurochemical level, VPA-exposed rats displayed altered phosphorylation of CB1 cannabinoid receptors in different brain areas, associated with changes in anandamide metabolism from infancy to adulthood. Interestingly, enhancing anandamide signaling through inhibition of its degradation rescued the behavioral deficits displayed by VPA-exposed rats at infancy, adolescence and adulthood. This study therefore shows that abnormalities in anandamide activity may underlie the deleterious impact of environmental risk factors on ASD-relevant behaviors and that the endocannabinoid system may represent a therapeutic target for the core and associated symptoms displayed by autistic patients.”

Wei D, Dinh D, Lee D, Anguren A, Moreno-Sanz G, et al. Enhancement of anandamide-mediated endocannabinoid signaling corrects autism-related social impairment. *Cannabis and Cannabinoid Research* 2016;1:1, 81-89, DOI:10.1089/can.2015.0008.

Effect of administering an inhibitor of the enzyme that degrades the endocannabinoid AEA was tested on two distinct mouse models of ASD. The two models were a strain with a mutation that models human Fragile-X Syndrome and the BTRT mouse strain – an inbred strain with behaviors similar to ASD not known to be caused by a mutation. Social impairment was tested with a previously established method: the three-chambered social approach task. First the mice were habituated to the center chamber for ten minutes with the doors to the other two chambers closed. Then the mice were tested in a ten-minute session. Subjects were offered a choice between a novel object and a novel mouse in opposing side chambers. The novel object was a clear, empty inverted pencil cup and the novel social stimulus mouse was a sex, age, and weight-matched mouse constrained by a clear, empty inverted pencil cup. Chamber time scoring was automated using image analysis. Sniffing time was scored by trained assistants who were unaware of treatment conditions. Administration of a drug that inhibits FAAH, an enzyme that degrades AEA, completely reversed the social impairment found in both strains.

Clinical Trials

No randomized, controlled clinical trials have been completed for cannabis or cannabinoids as therapy for ASD. However, two have been registered on www.clinicaltrials.gov and are now under way (see descriptions below). Though internet blogs and discussion forums have numerous accounts of use of cannabis and cannabinoids in persons with autism, the following case history was the only publication found for therapeutic use of a cannabinoid or cannabis product for autism.

Kurz R, Blaas. Use of dronabinol (delta-9-THC) in autism: a prospective single- case-study with an early infantile autistic child. *Cannabinoids* 2010;5:4-6.

In this study, synthetic delta-9-THC (dronabinol) was studied as a supplemental therapy in an autistic Austrian child. The child at the center of this study was diagnosed with early infantile autism at the age of three. He was six years old when the study was conducted. The study lasted six months. During the study period, the child initially received dronabinol drops at a dosage of one drop every morning (0.62 mg THC). On a day-to-day basis, the dosage was gradually increased, reaching a maximum tolerated dose of 3.62 mg THC per day (two drops in the morning, one drop at midday, and three evening drops).

At the end of the six months, the boy's symptom severity significantly decreased in five different categories: hyperactivity, lethargy, irritability, stereotypic behavior, and inappropriate speech. Based on these findings, the authors argue that dronabinol may be a therapeutic for treating early infantile autism. Dronabinol may not replace other therapies, but it is a potential, additional therapy. Larger, controlled studies on cannabinoids and autism are needed to further understand their findings, say the authors.

Cannabinoids for Behavioral Problems in Children with ASD (CBA): NCT02956226 (registered on www.clinicaltrials.gov)

This is a double blind randomized placebo-controlled clinical trial of two cannabis formulations to treat disruptive behaviors in children and young adults (age 5-21) with ASD. It is being carried out in Israel. Estimated enrollment is 120 patients, who will be assigned to one of three olive oil-based solutions for a three-month treatment period: 1) 99% CBD and 99% THC in a ratio of 20:1 CBD:THC; 2) whole plant extract with a CBD:THC ratio of 20:1; or, 3) placebo. Primary outcome is change from baseline Home Situations Questionnaire-Autism Spectrum Disorder score, at 3 months (it is a 24-item parent-rated measure of noncompliant behavior in children with ASD). There are several other outcome measures. Recruitment began January, 2017. Estimated study completion date is July, 2019.

Cannabidivarin (CBDV) vs. Placebo in Children with Autism Spectrum Disorder (ASD): NCT03202303 (registered on www.clinicaltrials.gov)

This double blind placebo-controlled clinical trial of CBDV to treat children (age 5-18 years) will be carried out in New York City. Estimated enrollment is 100 patients, who will be assigned to either 800 mg/day (400 mg twice/day) CBDV or placebo capsule for a 12-week treatment period. Primary outcome is change from baseline Aberrant Behavior Checklist-Irritability Subscale, at 12

weeks. There are several other outcome measures. Recruitment will begin October, 2017. Estimated study completion date is September, 2021.

Observational Studies

De Alwis D, Agrawal A, Reiersen AM, Constantino JN, Henders A, Martin NG, & Lynskey MT. ADHD symptoms, autistic traits, and substance use and misuse in adult Australian twins. *J Stud Alcohol Drugs* 2014;75:211-221.

Substance use among people with autism spectrum disorders (ASD) is hypothesized to be rare, since those with ASD lack the social skills that would bring them into contact with others who use drugs and since people with ASD have less novelty-seeking behaviors than average. However, there are few studies to test this hypothesis. This study uses a cross-sectional interview and self-reported questionnaire to elucidate the relationship between people with autism traits, substance use, and substance abuse. The interview and questionnaire's study sample size was 3,028 white, Australian twins born between 1972 and 1979. The study participants' drug use, abuse, and misuse were assessed through the interview. The self-reported questionnaire collected data on the participants' autistic traits.

Surprisingly, the results of the analysis indicate that cannabis use is associated with having autistic traits in a statistically significant manner. Cannabis abuse/dependence were also significantly associated with high levels of autistic traits.

Several factors limit interpretation of this finding, however. From a demographic perspective, the study sample is racially homogenous, and its findings may not be replicated in more diverse study samples. Causal relationships cannot be determined because of the study's cross-sectional design. Last, formal diagnostic criteria were not used to determine an autism spectrum disorder diagnosis: only autistic traits were studied.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of autism spectrum disorder were found.

References

American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5th ed.)*. Arlington, VA: American Psychiatric Publishing, 2013.

Buescher AV, Cidav Z, Knapp M, Mandell DS. Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA Pediatr* 2014;168:721-728.

Christensen DL, Baio J, Van Naarden BK, Bilder D, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2012. *MMWR Surveill Summ* 2016;65:1-23.

De Alwis D, Agrawal A, Reiersen AM, Constantino JN, Henders A, Martin NG, Lynskey MT. ADHD symptoms, autistic traits, and substance use and misuse in adult Australian twins. *J Stud Alcohol Drugs* 2014;75:211-221.

Doenni VM, Gray JM, Song CM, Patel S, Hill MN, Pittman QJ. Deficient adolescent social behavior following early-life inflammation is ameliorated by augmentation of anandamide signaling. *Brain Behav Immun* 2016;58:237-247.

Dove D, Warren Z, McPheeters ML, Taylor JL, Sathe NA, Veenstra-VanderVeele J. Medications for adolescents and young adults with autism spectrum disorders: A systematic review. *Pediatrics* 2012;130:717-726.

Hanley GP, Iwata BA, Thompson RH. Reinforcement schedule thinning following treatment with functional communication training. *J Applied Behav Anal* 2001;34:17-38.

Harrington JW, Allen K. The clinician's guide to autism. *Pediatr Rev* 2014;35:62-78.

Kurz R, Blaas K. Use of dronabinol (delta-9-THC) in autism: a prospective single-case-study with an early infantile autistic child. *Cannabinoids* 2010;5:4-6.

Lovaas, O. I. Behavioral treatment and normal educational and intellectual functioning in young autistic children. *J Consult Clin Psychol* 1987;55:3-9.

McPheeters ML, Warren Z, Sathe N, Bruzek JL, Krishnaswami S, Jerome RN, Veenstra-VanderWeele J. A systematic review of medical treatments for children with autism spectrum disorders. *Pediatrics* 2011;127:e1312-e1321.

Ospina MB, Seida JK, Clark B, Karkhaneh M, Hartling L, Tjosvold L, et al. Behavioural and developmental interventions for autism spectrum disorder: a clinical systematic review. *PloS One* 2008;3(11), e3755.

Servadio M, Melancia F, Manduca A, di Masi A, Schlavi S, et al. Targeting anandamide metabolism rescues core and associated autistic-like symptoms in rats prenatally exposed to valproic acid. *Transl Psychiatry* 2016;6 e902 doi:10.1038/tp.2016.182.

Taylor JL, Dove D, Veenstra-VanderWeele J, Sathe NA, McPheeters ML, Jerome RN, Warren Z. Interventions for adolescents and young adults with autism spectrum disorders. *Comparative Effectiveness Review*, Agency for Healthcare Research and Quality (US) 2012;65.

Warren Z, McPheeters ML, Sathe N, Foss-Feig JH, Glasser A, Veenstra-VanderWeele J. A systematic review of early intensive intervention for autism spectrum disorders. *Pediatrics* 2011;127:e1303-1311.

Wei D, Dinh D, Lee D, Anguren A, Moreno-Sanz G, et al. Enhancement of anandamide-mediated endocannabinoid signaling corrects autism-related social impairment. *Cannabis and Cannabinoid Research* 2016;1:1, 81-89, DOI:10.1089/can.2015.0008.

White SW, Keonig K, Scahill L. Social skills development in children with autism spectrum

disorders: A review of the intervention research. *J Autism Dev Disord* 2007;37:1858-1868.
Zamberletti E, Gabaglio M, Parolaro D. The endocannabinoid system and autism spectrum disorders: Insights from animals. *Int J Mol Sci* 2017;18(9). pii: E1916. doi: 10.3390/ijms1809191

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