MDH Minnesota Department of Health
OFFICE OF MEDICAL CANNABIS

# Autism Spectrum Disorder (ASD)

AUGUST 2016

## 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, clinicatrials.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 (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).

The Diagnosis 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 (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:
    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 (Christensen, 2016). 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 (Harrington and Allen, 2014). 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 et al., 2014).

## Current Therapies

Several behavioral, educational, and pharmaceutical treatments exist to treat ASD (Harrington and Allen, 2014; Ospina et al., 2008). Pharmaceutical treatments mostly target comorbid health problems, which are common in children living with ASD (McPheeters et al., 2011).

Behavioral and developmental interventions are the primary treatments for ASD (Ospina et al., 2008). There is a great variety in the kinds of behavioral and developmental interventions, which are organized into smaller subcategories (Ospina et al., 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 and Allen, 2014; Ospina et al., 2008). Another kind of behavior and developmental intervention is social skills training (SST), which targets social deficits (White and Koenig, 2007).

ABA-based therapies have demonstrated positive effects on language, adaptive, cognitive, and educational outcomes (Hanley, Iwata, & Thompson, 2001; Lovaas, 1987; Warren et al., 2011). However, there is a lack of high-quality randomized controlled trials (Warren et al., 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 et al., 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 and Koenig, 2007).

Common comorbidities in children with ASD include intellectual disability, constipation, sleep disorders, anxiety, ADHD, and seizure disorders (Harrington and Allen, 2014; McPheeters et al., 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 and Allen, 2014). Antipsychotic medications, serotonin-reuptake inhibitors, and stimulants are among the pharmaceuticals used to treat mental-health comorbidities (McPheeters et al., 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 et al., 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 et al., 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 et al., 2012). There is a dramatic lack of evidence on the best way to treat adolescents and young adults who have ASD (Dove et al., 2012; Taylor et al., 2012).

## Pre-Clinical Research

Few pre-clinical research publications focusing on the endocannabinoid system and aspects of the neurologic system specific to ASD were found – perhaps because so little is known about the causes of ASD. The following publication reports on studies of mice with the Fragile X gene mutation. Fragile X syndrome in humans is the most commonly known genetic cause of autism.

**Jung KM, Sepers M, Henstridge, Lassalle, et al. Uncoupling of the endocannabinoid signaling complex in a mouse model of fragile X syndrome. *Nature Communications* 2012;3:1080 doi: 10.1038/ncomms2045.**

This highly technical article presents three lines of experimental evidence suggesting the protein missing because of the Fragile X gene mutation, FMRP, is required for normal operations of the endocannabinoid system. Specifically, FMRP appears to be necessary for normal production and release of 2-AG, an endocannabinoid considered important for brain development and functioning.

# Clinical Trials

No randomized, controlled clinical trials have been completed for cannabis product therapies and ASD and none underdevelopment were found on www.clinicaltrials.gov. 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, K. (2010). Use of dronabinol (delta-9-THC) in autism: a prospective single-case-study with an early infantile autistic child.Cannabinoids, 5(4), 4-6.**

In this study, purified 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.

# Observational Studies

**De Alwis, D., Agrawal, A., Reiersen, A. M., Constantino, J. N., Henders, A., Martin, N. G., & Lynskey, M. T. (2014). ADHD symptoms, autistic traits, and substance use and misuse in adult Australian twins. Journal of studies on alcohol and drugs, 75(2), 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.

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.

Jung KM, Sepers M, Henstridge, Lassalle, et al. Uncoupling of the endocannabinoid signaling complex in a mouse model of fragile X syndrome. *Nature Communications* 2012;3:1080 doi: 10.1038/ncomms2045.

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.

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.*

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.

Minnesota Department of Health
Office of Medical Cannabis
PO Box 64882,
St. Paul, MN (zip) 55164-0882
(phone) 651-201-5598
Health.Cannabis@state.mn.us
www.health.state.mn.us

MDH
Minnesota Department *of* Health

*To obtain this information in a different format, call: 651-201-5598. Printed on recycled paper.*