Utah Department of
Health & Human Services
Center for Medical Cannabis

Department of Health and Human Services

Guidance on the Suggested Use of Medical Cannabis

Autism

About this document: The following information on the use of medical cannabis serves as a suggested use guide for those participating in the Utah Medical Cannabis Program. The intended audience for this document includes qualified medical providers, pharmacy medical providers, patients intending to use medical cannabis, and caregivers of patients intending to use medical cannabis.

This document details the guidance on the use of medical cannabis for autism spectrum disorder. This document does not include general instructions on the use of medical cannabis, contraindications, warnings, precautions and adverse reactions to using cannabis and drug-to-drug interactions which could be found in the extended guidance document titled *Guidance on the Suggested Use of Medical Cannabis.* The extended guidance document can be found on the Department of Health and Human Services Center for Medical Cannabis website (www.medicalcannabis.utah.gov).

About the authors: This document was authored by the Utah Cannabis Research Review Board and Department of Health and Human Services staff.

About the Utah Cannabis Research Review Board: Under Utah Health Code 26-61-201, the Cannabis Research Review Board is a board of medical research

professionals and physicians who meet on a voluntary basis to review and discuss any available scientific research related to the human use of cannabis, cannabinoid product or an expanded cannabinoid product that was conducted under a study approved by an Institutional Review Board (IRB) or was conducted and approved by the federal government.

This document has been updated from its original form and all changes were approved and voted on June 8, 2021 by the Cannabis Research Review Board.

DISCLAIMER

The following information on the use of medical cannabis serves as a suggested use guide for those participating in the Utah Medical Cannabis Program. This document has been vetted and approved by the Utah Cannabis Research Review Board under Utah Health Code 26-61-202.

This document is a summary of available peer-reviewed literature concerning potential therapeutic uses and harmful effects of cannabis and cannabinoids. With the ongoing nature of cannabis and cannabinoid research, it is not meant to be complete or comprehensive and should be used as a limited complement to other reliable sources of information. This document is not a systematic review or meta-analysis of the literature and has not rigorously evaluated the quality and weight of the available evidence. There is a lack of controlled clinical trials yielding high level evidence of predictable therapeutic benefit for any given condition other than those for FDA approved formulations. This document includes warnings and risks related to the use of cannabis including cannabis use disorder, potentially irreversible brain damage/mental illness, and legal liability for DUI and potential for adverse work-related consequences.

All patrons participating in the Utah Medical Cannabis Program are advised to use this document and any such document produced from this original document as informational and educational. The use of medical cannabis is at one's own risk. **Medical cannabis is NOT a first line therapy for most medical conditions.**

The information in this document is intended to help as far as available data allows Utah health care decision-makers, health care professionals, health systems leaders, and Utah Medical Cannabis patients to make well-informed decisions and thereby improve the quality of health care outcomes in patients using medical

cannabis use. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process.

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IMPORTANT NOTE: As always, in the event of significant side effects, stop use of medical cannabis until side effects have resolved, and then reduce to previous, best-tolerated dose. To avoid unwanted psychoactive side effects, **"start low and go slow"** especially when using cannabis products for the first time or using new dosages or types of products.

There is insufficient evidence to support or refute the conclusion that medical cannabis or cannabinoids are effective or ineffective in the treatment of comorbid symptoms of agitation in individuals with autism spectrum disorder.

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The **core diagnostic features** of Autism Spectrum Disorder (ASD) (American Psychiatric Association) include:

1. Persistent deficits in social communication and social interactions including difficulty communicating thoughts and feelings, deficits in social-emotional reciprocity, non-verbal communication, and adjusting behaviors to suit variable social contexts;
2. Restricted, repetitive interests or behaviors; and
3. Onset during childhood

ASD may be accompanied by **comorbid symptoms** and conditions including:

1. Agitation (self-injury, disruptive behaviors)
2. Disrupted sleep
3. Feeding issues
4. Co-occurring psychiatric symptoms/diagnoses (anxiety, specific phobia, obsessive compulsive disorder, ADHD, major depressive disorder, oppositional defiant disorder, psychotic disorders)
5. Epilepsy

As of March 2021, there is **no evidence** from clinical trials to support the conclusion that medical cannabis or cannabinoids are useful or effective in the **treatment of the core symptoms** of ASD

There are **limited observational reports** (Aran et al., 2018; Schleider et al., 2019; Barchal et al., 2019) and **one placebo-controlled trial** (Aran et al. 2021) showing possible short-term benefits of an orally-administered cannabidiol-predominant cannabis extract preparation with a CBD:THC ratio of 20:1, in the **treatment of comorbid problems** with agitation and other severe behaviors in children and young adults with ASD that have been refractory to standard treatments.

There are **no clinical data regarding the long-term safety or efficacy** of cannabis or cannabinoids in the treatment of comorbid symptoms of agitation or other severe behavioral problems in individuals with ASD.

Based on very limited short-term clinical data outlined above, and no clinical studies looking at long-term efficacy or safety, the Cannabis Research Review Board concludes that currently **there is insufficient evidence to support or refute the conclusion that medical cannabis or cannabinoids are effective or ineffective in the treatment for comorbid symptoms of agitation in individuals with autism spectrum disorder.**

Comorbid agitation and other severe behavioral problems in individuals with ASD can be challenging to manage and may not adequately respond to non-pharmacologic, and FDA-approved pharmacologic interventions. Because of the severity of symptoms, lack of adequate response, and side-effects from other treatments, some individuals and/or their caretakers may consider using cannabis-based products for the management and control of agitation and complex

behavioral problems associated with ASD that are not adequately managed with usual treatments.[1]

If the decision is made to attempt to manage agitation and other complex behavioral problems in an individual with ASD using cannabis/cannabinoid preparations, the healthcare provider, the individual (if possible), and their caretakers should understand the following prior to proceeding:

1. There are no clinical trials evaluating the long-term effectiveness and safety of using any cannabis-based medicines in the treatment of agitation associated with ASD;
2. Use of cannabinoid products containing THC during critical periods of child and adolescent brain development may result in short-term and/or long-term adverse effects on neurocognitive functions including learning, memory, and attention (Dharmapuri et al., 2020; Schonhofen et al., 2018);
3. Use of cannabis-based medicines containing THC may result in the development of psychosis which may or may not be reversible (Dharmapuri et al., 2020; Schonhofen et al., 2018);
4. Individuals with ASD may be more likely to develop cannabis-related psychosis than those who do not have ASD;
5. The onset of psychosis due to THC may not be immediate and may not show up for months to years after starting treatment with THC-containing cannabis preparations;
6. Detection of symptoms of psychosis due to the use of THC-containing cannabis preparations in individuals with ASD may be delayed and be more difficult to detect due to the core problems with communication that characterize individuals with ASD;
7. There may be undiagnosed underlying conditions feeding comorbid symptoms of agitation in individuals with ASD that may respond to appropriate non-cannabinoid interventions, sparing the costs and risks of the unnecessary use of cannabis/cannabinoids;
8. The single placebo-controlled study that showed possible benefit of using a cannabis extract in management of comorbid agitation associated with ASD used a CBD-predominant oral preparation containing a CBD:THC ratio of 20:1 (Aran et al., 2021);

[1] Epilepsy is a known comorbidity of ASD, and in some cases CBD has been used to decrease the frequency of seizures. The use of CBD and/or THC for comorbidities of ASD should be assessed on a case-by-case basis and separately from ASD. More information on suggested use of cannabis as a medical treatment for epilepsy can be found on the Cannabis Research Review Board's website (https://medicalcannabis.utah.gov/resources/cannabinoid-product-board/) in the CRRB guidance document for epilepsy.

Based on observational data and the single placebo-controlled trial referenced above, the following may be considered as a possible starting point for use of medical cannabis for treatment of comorbid agitation in individuals with ASD:

- Suggested chemotype: Chemotype III, CBD predominant (20:1) CBD:THC ratio
- Dose form: Cannabis extract prepared for oral or sublingual use
- Route: Sublingual drops
- Starting dose and titration: Dose range for efficacy is likely quite variable depending on unknown or unpredictable individual patient factors. In the placebo controlled trial the following dose titration regimen was used (Aran et al., 2021):

  Starting dose: 1 mg/kg/d CBD (and 0.05 mg/kg/d THC).

  Titration: increase dose 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.

  Maximum dose: 420 mg CBD and 21 mg THC per day divided into 3 daily doses.
- Slower, more gradual up-titration than every 2 days, with careful monitoring for adverse reactions and desired clinical outcomes, may be more appropriate in real-world nonclinical-trial settings.
- Careful monitoring for difficult-to-detect adverse reactions from use of cannabis-based products including psychosis, should be done by a provider with clinical expertise assessment and management of patients with ASD and comorbid conditions.

RECOMMENDATIONS: The Cannabis Research Review Board ***recommends against the use of cannabinoid products containing high amounts of THC in individuals with ASD*** due to the pre-existing increased risk of psychosis in individuals with ASD, and lack of any clinical data supporting the use of cannabis products containing high amounts of THC in individuals with ASD.

The Cannabis Research Review Board ***recommends caution when using cannabidiol, or cannabidiol-predominant cannabis products for the treatment of comorbid symptoms of ASD due to the lack of data regarding long-term risks and benefits of such use in individuals with ASD***.

There is insufficient evidence to support or refute the conclusion that medical cannabis or cannabinoids are effective or ineffective in the treatment of comorbid symptoms of agitation in individuals with autism spectrum disorder.

With the higher CBD doses use caution and monitor for: fatigue, somnolence, sedation, depression, suicidality, also monitor liver function tests, drug interactions with other anticonvulsants and concomitant use with Epidiolex (30% of patients have comorbid seizures) is not recommended (Viner, 2019).

Cannabis use in children, adolescents, and adults under the age of 26 may result in altered brain development and function with ***possible long-term negative consequences*** including negative mental health outcomes and long-term cognitive impairments (Meier et al., 2012; Brumback et al., Morin et al., 2019).

Use of cannabis or cannabinoids for treatment of various conditions under the age of 26 ***should be considered only after failure of robust treatment attempts using conventional interventions and then only after a careful risk/benefit assessment and discussion with the patient or patient's guardian(s).*** A recent systematic review of the use of medical cannabis in children may be helpful when considering the use of medical cannabis in the pediatric population (Wong & Wilens, 2017).

References:

Aran, A., Cassuto, H., Lubotzky, A., Wattad, N., & Hazan, E. (2018). Brief report: Cannabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems—a retrospective feasibility study. *Journal of Autism and Developmental Disorders, 49*(3), 1284-1288. doi:10.1007/s10803-018-3808-2

Aran, A., Harel, M., Cassuto, H., Polyansky, L., Schnapp, A., Wattad, N., . . . Castellanos, F. X. (2021). Cannabinoid treatment for autism: A proof-of-concept randomized trial. *Molecular Autism, 12*(1). doi:10.1186/s13229-021-00420-2

Bar-Lev Schleider, L., Mechoulam, R., Saban, N., Meiri, G., & Novack, V. (2019). Real life experience of medical cannabis treatment in autism: Analysis of safety and efficacy. *Scientific Reports, 9*(1). doi:10.1038/s41598-018-37570-y

Barchel, D., Stolar, O., De-Haan, T., Ziv-Baran, T., Saban, N., Fuchs, D. O., . . . Berkovitch, M. (2019). Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and comorbidities. *Frontiers in Pharmacology, 9*. doi:10.3389/fphar.2018.01521

Brown, C. (2012). A phase iia clinical trial to demonstrate proof of concept of an experimental pediculicide lotion for the treatment of head lice. *Http://isrctn.org/*. doi:10.1186/isrctn66611560

Brumback, T., Castro, N., Jacobus, J., & Tapert, S. (2016). Effects of Marijuana Use on Brain Structure and Function. International Review of Neurobiology Imaging the Addicted Brain, 33–65. doi: 10.1016/bs.irn.2016.06.004

Dharmapuri, S., Miller, K., & Klein, J. D. (2020). Marijuana and the pediatric population. *Pediatrics, 146*(2). doi:10.1542/peds.2019-2629

Di Forti, M., Quattrone, D., Freeman, T. P., Tripoli, G., Gayer-Anderson, C., Quigley, H., . . . Van der Ven, E. (2019). The contribution of cannabis use to variation in the incidence of psychotic DISORDER across Europe (eu-gei): A multicentre case-control study. *The Lancet Psychiatry, 6*(5), 427-436. doi:10.1016/s2215-0366(19)30048-3

Diagnostic and statistical manual of mental disorders: DSM-5. (2019). In *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed., pp. 50-59). American Psychiatric Association.

Manrique-Garcia, E., Zammit, S., Dalman, C., Hemmingsson, T., Andreasson, S., & Allebeck, P. (2014). Prognosis of schizophrenia in persons with and without a history of cannabis use. *Psychological Medicine, 44*(12), 2513-2521. doi:10.1017/s0033291714000191

Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S. E., … Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. Proceedings of the National Academy of Sciences, 109(40). doi: 10.1073/pnas.1206820109

Morin, J.-F. G., Afzali, M. H., Bourque, J., Stewart, S. H., Séguin, J. R., O'LearyBarrett, M., & Conrod, P. J. (2019). A Population-Based Analysis of the Relationship Between Substance Use and Adolescent Cognitive Development. American Journal of Psychiatry, 176(2), 98–106. doi: 10.1176/appi.ajp.2018.18020202

Schonhofen, P., Bristot, I. J., Crippa, J. A., Hallak, J. E., Zuardi, A. W., Parsons, R. B., & Klamt, F. (2018). Cannabinoid-based therapies and brain development: Potential harmful effect of early modulation of the endocannabinoid system. *CNS Drugs, 32*(8), 697-712. doi:10.1007/s40263-018-0550-4

Viner, M. W. (2019). Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds. Retrieved from https://www.regulations.gov/comment/FDA-2019-N-1482-0309

Wong, S. S., & Wilens, T. E. (2017). Medical Cannabinoids in Children and Adolescents: A Systematic Review. Pediatrics, 140(5). doi: 10.1542/peds.2017-1818