The Honorable Senator Jim Smallwood, Chair
Senate Committee on Health and Human Services
State Capitol, Room 354
Denver, CO 80203

April 19, 2018

Re: HB 1263 – Adding Autism Spectrum Disorder to List of Disabling Conditions for Medical Marijuana Use

Dear Mister Chair and Members of the Committee:

On behalf of American Academy of Pediatrics Colorado Chapter, Children's Hospital Colorado, Colorado Academy of Family Physicians, Colorado American College of Emergency Physicians, Colorado Child and Adolescent Psychiatric Society, Colorado Medical Society, Colorado Psychiatric Society, Colorado Society of Osteopathic Medicine and Denver Health, we respectfully request your opposition today to House Bill 1263, regarding medical marijuana use for autism spectrum disorder (ASD). Our concerns with this legislation, outlined below, fall into two categories: process and policy.

Regarding process, our utmost concern is that the changes outlined in HB 18-1263 circumvent the voter-approved process defined by our state Constitution for adding new conditions approved for medical marijuana use. Section 14 of Article XVIII of the Colorado Constitution lists a range of debilitating medical conditions approved for medical marijuana use. Language in this section adds the following to the definition of debilitating medical conditions approved for medical marijuana use: *(III) Any other medical condition, or treatment for such condition, approved by the state health agency, pursuant to its rule making authority or its approval of any petition submitted by a patient or physician as provided in this section.*

Colorado Department of Public Health and Environment (the Department) rules (5 CCR 1006-2) clearly define the process for a physician or patient petition to add a disabling condition, including direction and a timeline for the Department to review the petition, conduct a search of peer-reviewed published medical literature to support the petition request and present findings. It concerns us that the condition outlined in HB 18-1263, autism spectrum disorder, has never gone through the petition process for scientific review at the Department, as voters expected would happen when they approved medical marijuana at the ballot.

In terms of our policy concerns, first and foremost, the science surrounding marijuana exposure to the developing brain demonstrates that marijuana is harmful to attention, cognition, executive control, memory, problem-solving and more. While this evidence base pertains to adolescent brain development in particular, it is possible that even younger children could be at risk for suboptimal brain development. This concerns us, given that if this bill were to pass, marijuana would be available to youth with autism spectrum disorder. Further, there are currently no peer-reviewed published human studies with a focus on children with autism spectrum disorder and medical marijuana use. We wholeheartedly support research to assess the efficacy of cannabis as a treatment modality for autism spectrum disorder. However, by adding autism spectrum disorder at this time to the list of conditions approved for medical marijuana use, HB18-1263 forgoes standard medical protocol of proof of efficacy when exposing children to a new substance. We appreciate the bill proponents' willingness to work with us regarding

an amendment to encourage and promote additional scientific research within the Colorado Department of Public Health's current Medical Marijuana Scientific Research Grant program. Additional research, specifically focusing on pediatric populations, is valuable to inform both policy initiatives and clinical treatments.

Furthermore, autism spectrum disorder is a developmental disorder, and evidence shows us that the best treatments include early intervention, behavioral therapy and other therapies such as speech, occupational and physical therapy. Traditional or alternative medications are not the clinically preferred method of treatment, and reliance on these approaches at the expense of evidence-based therapies will lead to worse developmental outcomes for these children, their families and taxpayers.

As compassionate caregivers, we empathize with patients and families who are looking to complementary and alternative treatments for relief. We fully support research in these areas to determine the viability, benefits and risks of cannabis products as a treatment modality. As medical professionals who use peer-reviewed, evidence-based data to evaluate, diagnose and treat patients, we cannot support HB18-1263, as it lacks demonstrated benefit and low risk of harm for children and youth with autism spectrum disorder. Thank you for the opportunity to comment on this proposed legislation, and please do not hesitate to contact us if you have any questions regarding our opposition to it.

Sincerely,

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DEPARTMENT OF HEALTH

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, 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. 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 206, 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 endocannainoid 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 pateints.

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 it 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 fomulations 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 Autsim 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.

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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.

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Medical Marijuana: Review of the Science and Implications for Developmental Behavioral Pediatric Practice

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Abstract

Marijuana policy is rapidly evolving in the United States and elsewhere, with cannabis sales fully legalized and regulated in some jurisdictions and use of the drug for medicinal purposes permitted in many others. Amidst this political change, patients and families are increasingly asking whether cannabis and its derivatives may have therapeutic utility for a number of conditions, including developmental and behavioral disorders in children and adolescents. This review examines the epidemiology of cannabis use among children and adolescents, including those with developmental and behavioral diagnoses. It then outlines the increasingly well-recognized neurocognitive changes shown to occur in adolescents who use cannabis regularly, highlighting the unique susceptibility of the developing adolescent brain and describing the role of the endocannabinoid system in normal neurodevelopment. The review then discusses some of the proposed uses of cannabis in developmental and behavioral conditions, including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Throughout, the review outlines gaps in current knowledge and highlights directions for future research, especially in light of a dearth of studies specifically examining neurocognitive and psychiatric outcomes among children and adolescents with developmental and behavioral concerns exposed to cannabis.

Keywords

adolescent; cannabis; marijuana abuse; attention deficit disorder with hyperactivity; child development disorders; pervasive

In the United States and throughout the world, marijuana policy is rapidly evolving.[1-3] In many jurisdictions, marijuana is now decriminalized, meaning that possession of the drug does not lead to criminal charges.[4] In others, its use is permitted for medical purposes if a license or permit is issued to a patient or caregiver.[5] In others still, including Washington

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Conflict of Interest Statement: The authors have no conflicts of interest to disclose.

State and Colorado, as well as in the country of Uruguay, marijuana sales for recreational use among adults are now fully legal and regulated by the government.[6,7]

Many of these dramatic policy changes have occurred within the last decade, and amidst this shifting political landscape, patients and families are increasingly asking whether marijuana – often used interchangeably in the literature and in the present article with the term cannabis – has a role in the management of developmental and behavioral pediatric conditions, including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD), among others.[8,9] This is occurring despite a dearth of scientific evidence supporting a role for cannabis in these conditions. Some of this interest in cannabis has been fueled by the lay press, which has recently showcased rare examples of children with certain medical conditions who had failed traditional pharmacologic management and for whom cannabis was seemingly the only effective treatment.[9,10] Accordingly, children and adolescents are increasingly being added to medical marijuana registries by their parents for a multitude of conditions.[11]

Despite an absence of known efficacy of cannabis for developmental and behavioral conditions, there is indeed mounting evidence for its role in some neurological symptoms. A recent systematic review[12] of adult patient trials showed that certain formulations of cannabinoids were useful for spasticity and central pain. This same review concluded that data were insufficient to conclude efficacy in a number of other conditions, including Tourette syndrome, epilepsy and dystonia. Nonetheless, anecdotal evidence suggests that certain forms of marijuana, namely those enriched with cannabidiol (one of the many cannabinoid compounds present in cannabis but which does not have psychoactive properties), reduces the frequency of seizures for certain children with intractable epilepsy.[13] This anecdotal evidence is not yet supported by clinical trial data, as highlighted by a recent Cochrane review of adult studies on the subject,[14] but future studies will inevitably study this further.

Clearly, some parents are already using or are considering using cannabis for treatment of a wide range of pediatric conditions. Given the increasing prevalence of adolescent cannabis misuse and dependence,[15-17] as well as the growing body of literature linking cannabis use to long-term and potentially irreversible adverse physical, neurocognitive, psychiatric and psychosocial outcomes,[18] it is now more important than ever for the developmental-behavioral pediatrician to understand the available evidence on cannabis. Large professional organizations, including the American Academy of Pediatrics,[19] the American Medical Association,[20] the American Society of Addiction Medicine,[21,22] and the American Academy of Child and Adolescent Psychiatry[23] all have policy statements identifying marijuana use as a public health concern and currently oppose further steps towards legalization.

Here, we begin by describing important pharmacodynamic properties of cannabinoids, and then report the epidemiology of cannabis use, including the susceptibility of youth with developmental and behavioral disorders to earlier and heavier substance use. We then describe the known adverse neurocognitive effects of cannabis, highlighting the unique vulnerability of the developing brain and emphasizing the role of the endocannabinoid

system in normal neurodevelopment. We conclude by reviewing some of the proposed uses of cannabis for developmental and behavioral conditions that have recently received attention, highlighting the knowledge gap that currently exists.

Pharmacology

Marijuana, also referred to as cannabis, is traditionally derived from the plant *Cannabis sativa*. The dried buds and accompanying leaves of cannabis are most commonly smoked, but can also be ingested, and increasingly, youth inhale it by vaporization (a process referred to as "vaping") through new delivery systems similar to those used for e-cigarettes.[24] Hash oil, which is illegal and contains a high concentration of cannabinoids, can be extracted from cannabis plant material and also can be smoked, ingested or vaporized.[25] (It is not to be confused with hemp oil, often sold legally in natural food stores, which contains very few if any cannabinoids.) Onset of physiologic and psychologic effects vary based on route of administration, with peak effects occurring 30 minutes after inhalation and two to four hours after ingestion.[26] Acute effects include on the one hand relaxation, euphoria, heightened perception, sociability, sensation of time slowing, increased appetite and decreased pain, and on the other hand, paranoia, anxiety, irritability, impaired short-term memory, poor attention and judgement, and poor coordination and balance.[26,27] Physiologic effects include tachycardia, hypertension, dry mouth and throat, and conjunctival injection.

Cannabis exerts its effects primarily through the compound Δ-9-tetrahydrocannabinol (THC) acting on endogenous cannabinoid receptors present through the central and peripheral nervous system.[28] THC is lipophilic, and readily crosses the blood-brain barrier and placenta.[29] Also owing to its lipophilicity, THC accumulates in fat and therefore has a long elimination half-life of several days to a week. Similarly, many of the byproducts of marijuana smoke are lipophilic, with as yet poorly understood effects on health and development.[30] The high fat solubility of many cannabinoids results in a large volume of distribution and long half-life of elimination from the body.[29] The ability of cannabinoids to cross the placenta and affect fetal neurodevelopment may underlie the observation that prenatal exposure to cannabis is associated with hyperactivity, impulsivity and inattention symptoms in childhood,[31] among other adverse.cognitive and behavioral outcomes summarized in a recent review.[32]

Potential health effects of cannabis may be exacerbated by the doubling of THC concentration in marijuana preparations that has occurred in the last two decades.[25] In recent years, numerous synthetic cannabinoids, often marketed as herbal mixtures and referred to as "Spice", "K2" or "Kronic", have been synthesized and sold for recreational purposes (often through the Internet), and the rapidity of their development and distribution has outpaced attempts to classify them as Schedule I substances in the US.[33]

Legal formulations also exist in several jurisdictions, including some in the US. Dronabinol and nabilone, both synthetic THC-based cannabinoids, are US Food and Drug Administration-approved and marketed for use for children and adults as an antiemetic in chemotherapy and as an appetite stimulant. As outlined earlier, cannabinoids without psychoactive properties, such as cannabidiol, are also increasingly receiving attention since

they may impart medicinal benefits with fewer psychologic effects, but remain poorly understood and require more study prior to approval and regulation. Nabiximols represents a combined THC and cannabidiol formulation administered as an oromucosal spray available outside the United States and used for alleviation of symptoms in multiple sclerosis.

Epidemiology

In the US and other developed countries, cannabis is the second most commonly used substance among adolescents after alcohol.[15-17,34] Three recurrent surveys track cannabis use in the US general adolescent population. Monitoring The Future (MTF)[16] and the Youth Risk Behavior Surveillance System (YRBSS)[15] are school-based surveys, and the National Survey on Drug Use and Health (NSDUH)[17] is a household-based survey. Collectively, the surveys demonstrate that as many as 4 in 10 adolescents have ever used marijuana, that prevalence of marijuana use is rising even as prevalence of alcohol and tobacco are falling (indeed, in 2009 cannabis use became more prevalent than tobacco use),[16] and that daily or near-daily use is becoming more common.[15-17] Specifically, daily use of marijuana is reported by 6.5% of high school seniors, 3.3% by 10th graders, and 1.2% by 8th graders, all of which represent an increase in prevalence of daily use occurring since 2008, previous to which daily use had been declining.[16] Use typically begins early in adolescence, with approximately 1 in 3 males and 1 in 4 females having tried marijuana by the 9th grade.[15]

In recent years, as the movement toward decriminalization and legalization of cannabis has progressed, adolescents' perceptions of the harms of marijuana have fallen. Indeed, since 2004, adolescents seeing "great risk" in regularly using marijuana has steadily fallen; in 2013, fewer than half of all 10th graders and high school seniors reported perceiving risk in regular use, whereas previously a majority of all adolescents had perceived risk.[16] Commensurate with this, emergency department visits related to marijuana increased 52% from 2004 to 2011 in the US.[35] Meanwhile, accidental ingestions by smaller children of cannabis preparations may be increasing, with ER visits at a Colorado pediatric hospital increasing from 0% (none reported) to 2.4% of all unintentional ingestions following change in state drug enforcement laws allowing possession of marijuana for medical purposes.[36] Calls made to Poison Control centers in the US have also been noted to increase in states where medical marijuana policies have been implemented or are underway.[37]

Data suggest that certain developmental-behavioral diagnoses portend higher risk of cannabis and other substance use and dependence. ADHD is a risk factor for earlier initiation of substance use in childhood and adolescence,[38-40] and may predict heavier and more problematic substance use in adolescence and adulthood.[41,42] Of all ADHD symptoms, hyperactivity and impulsivity confer the greatest risk for adolescent cannabis use disorder.[43] Although an early meta-analysis[44] showed that stimulant treatment for adolescent ADHD reduced the risk of subsequent substance use disorders, an updated meta-analysis incorporating newer studies with null findings suggests this may not be the case.[45] Oppositional defiant disorder (ODD), conduct disorder (CD), and ASD have all also been linked to problematic substance use, including of marijuana.[38,40,46] Among adolescents and adults with intellectual disability (ID), prevalence of cannabis and other substance use is not higher than for the general population, but risk for problematic use may be higher.[47,48] Data

from an adult study suggests that those with borderline or mild ID and with a comorbid psychiatric diagnosis are at even higher risk of a substance use disorder.[48]

Effects of Regular Marijuana Use on Neurocognition and Brain Structure

The high prevalence of marijuana use among adolescents, including those with developmental or behavioral disorders, is concerning given the myriad long-term consequences of regular cannabis use. Because of inconsistencies in how "regular" use is defined across studies, there is no clear indication as to whether there exists a 'safe' amount of cannabis use for adolescents. In general, "regular" use is defined in studies as daily or near-daily use over several years.[16] Regardless, in interpreting study results, it is important to recognize that because studies of cannabis use are observational in design, co-occurring use of alcohol, cigarettes or other drugs may confound reported associations, and reverse causality cannot always be excluded.[49] Although chronic marijuana use is associated with a broad range of adverse physical and mental health outcomes,[50-52] here we focus on the neurocognitive effects.[12,53]

Acute effects of marijuana intoxication vary by person and by dose. Positive effects reported by users include anxiolysis, euphoria, heightened perception, increased sociability, sensation of time slowing, increased appetite, and decreased pain.[26] On the surface, some of these effects may seem desirable to an adolescent with ADHD, although it is noteworthy that a study examining whether youth with ADHD used cannabis as a form of self-medication did not find this to be the case.[54] Negative effects of marijuana include paranoia, anxiety, irritability, worsened short term memory, poor attention, altered awareness of the passage of time, impaired judgement, decreased coordination and balance, and distorted spatial perception,[26,55] all of which could arguably exacerbate symptoms in developmental and behavioral conditions.

Clinicians should counsel youth that many of the detrimental neurocognitive effects of acute marijuana intoxication have a 'hangover' effect, with effects lasting at least one day after last use and with some subtle effects even measurable one month later among adolescent users.[56] Given the adverse effects of acute intoxication on attention, coordination and perception, it is perhaps unsurprising that a recent meta-analysis[57] demonstrated near doubling of the odds of fatal motor vehicle accident for adolescents and adults driving under the influence of cannabis. Data suggest that youth with ADHD are already at elevated risk of motor vehicle accident compared to the general adolescent population.[58-60] Therefore, counseling adolescents with ADHD to avoid driving while under the influence of marijuana is critical, particularly since many youth believe that marijuana does not affect their driving abilities.[61,62]

Over the long-term, adolescent cannabis use may be associated with a decline in intelligence quotient (IQ). A recent prospective study[63] showed that regular cannabis use during adolescence was followed by a significant decline in IQ at age 38 years, as illustrated in Figure 1. This finding persisted after adjusting for use of alcohol or other drugs, comorbid mental illness, and educational level. Additionally, among adolescents users who later became abstinent, cessation was not associated with restoration of IQ in adulthood. These

results are consistent with the possibility that cannabis impairs normal brain development during adolescence, and that heavy use may result in persistent and potentially non-reversible neurocognitive changes. A recent review[53] compiled studies on changes in cognition, brain structure and brain function among adolescent cannabis users; its summary of studies demonstrating an association between earlier age of marijuana initiation and worsened outcomes is shown in Table 1.

Regular cannabis use during adolescence is also associated with adverse psychiatric outcomes, although these psychiatric outcomes have not been rigorously studied among patients with developmental or behavioral concerns. A recent meta-analysis[64] and large, prospective cohort study[65] both reported increased odds of psychosis among adolescent cannabis users, an effect exacerbated by heavy use. Evidence linking adolescent cannabis use and depression are conflicting, with two recent systematic reviews[64,66] reporting an association, but acknowledging that adjustment for confounders may reduce or eliminate this association. A more recent prospective cohort study[67] of high school students demonstrated that heavy cannabis use was associated with later depression, but not suicidality. Another recent prospective study[68] showed that adolescent users have nearly triple the odds of an adult anxiety disorder, although a previous systematic review[64] examining adulthood anxiety among adolescent cannabis users reported conflicting data on this association. Figures 2a and 2b show the association of heavy cannabis use with psychosis and with depression, respectively, as reported by Moore *et al.* How the risk for subsequent psychiatric conditions differs among cannabis-using adolescents with developmental and behavioral concerns, in particular, is a critical area for further study.

To understand how these neurocognitive and psychiatric effects of cannabis might arise, two concepts are critical. First, as noted above, the psychoactive compound in cannabis, Δ-9-tetrahydrocannabinol (THC), is highly lipophilic and readily crosses the blood-brain barrier as well as the placenta, with implications for normal neurodevelopment in the marijuana-using adolescent as well as the developing fetus.[29] Second, the endocannabinoid system appears to play a significant role in normal neurodevelopment prenatally and extending throughout childhood and adolescence.[28] Cannabinoid receptors, which are normally activated by endogenous compounds such as anandamide, appear to modulate axonal migration and long-range subcortical projections in the brain during early brain development, and affect synaptic connectivity throughout childhood and adolescence.[69] Some of these developmental processes are known to occur throughout adolescence and into young adulthood, and alterations in these processes during critical windows are believed to result in permanent, irreversible deleterious effects.[70]

Although far from human application, data from rodents suggest that the endocannabinoid system may also be a potential target in developmental and behavioral conditions, though results remain conflicting.[71] Findings from rat models of Fragile X syndrome suggest that *blockade* of cannabinoid receptors may normalize aberrant hippocampal development, and simultaneously correct cognitive deficits, improve seizures, and reduce pain sensitivity.[72] Somewhat conflicting are additional findings from the same rat model showing that *enhancing* endocannabinoid signaling may correct abnormal synaptic plasticity occurring in

the prefrontal cortex and ventral striatum, with simultaneous improvement in hyperlocomotion and anxiety-related behaviors.[73]

Alterations in neurodevelopment from chronic cannabis use may underlie several known brain changes present in heavy-using adults. Functional imaging studies (using diffusion-weighted magnetic resonance imaging and brain connectivity mapping) show that axonal connectivity is impaired in regular marijuana users, particularly with early age of onset of use in adolescence.[74] Additionally, regular adult users who started cannabis use in adolescence exhibit decreased volume in the hippocampus and amygdala,[74,75] which are involved in memory processing, as well in other portions of the medial temporal cortex, temporal pole, parahippocampal gyrus, insula and orbitofrontal cortex, which have high concentrations of cannabinoid receptors and are responsible for motivational, emotional and affective processing.[76] The full extent of structural and functional neural changes from marijuana use is still not fully understood, and should be the focus of future study, particularly among adolescents with developmental and behavioral concerns, for whom study findings may differ from the general adolescent population.

Use of Marijuana for Pediatric Developmental and Behavioral Diagnoses

Understanding these long-term adverse consequences of cannabis use is especially important as patients and families question whether cannabis may have a role in managing pediatric conditions. Cannabis has had a broad range of proposed clinical applications (predominantly for adult conditions), including for symptomatic management of nausea, poor appetite, and pain, as well as for treatment of multiple sclerosis, spinal cord injury, glaucoma, Tourette syndrome, epilepsy and glaucoma.[77] At this time, good evidence is almost entirely lacking for its application in pediatric developmental and behavioral conditions. Nonetheless, online advocacy groups that support the use of 'medical' marijuana for such conditions are gaining popularity, particularly on social media sites such as Facebook. At the time of press, some examples include "Mothers for Medical Marijuana Treatment for Autism",[78] "Mothers Advocating Medical Marijuana for Autism (MAMMA)",[79] and "Pediatric Cannabis Therapy".[80]

Many advocates cite scientific literature regarding benefits of cannabis for the treatment of pediatric behavioral conditions, but often, data cited are from animal model-based research that does not yet have translation to human subjects. For example, a 2013 study[81] from Stanford University showed that mice with a specific and rare gene mutation linked to autism showed altered endocannabinoid signaling in the central nervous system. These data were then cited by online and print media supporters of medical marijuana (for example, the High Times[82]) as evidence that cannabis could be used as a treatment for autism. As another example, when another recent study[73] based on a mouse model of fragile X syndrome (described earlier in this review) showed alterations in endocannabinoid signaling pathways, these data were referenced (in this case, by more mainstream media outlets, such as the Huffington Post[83] and Fox News[84]) as evidence for a promising role for cannabis as treatment. Although these and other high-impact studies share important insights into the pathogenesis of ASD and fragile X syndrome, based on their results alone, it is erroneous

and potentially harmful to conclude that cannabis should be used as treatment for either of these disorders at this time.

With regard to human data on use of cannabis for developmental and behavioral conditions, to our knowledge, the only available data are from small case series or single studies. For example, one 6-year-old boy with autism was treated with daily dronabinol for six months and was noted to have improvement in hyperactivity, irritability, lethargy, stereotyped behaviors and speech, as measured by the Aberrant Behavior Checklist (ABC).[85] This single case study was uncontrolled and unblinded. In another single case study[86] of a cannabis-using adult male with ADHD off stimulants, the subject's driving skills in a simulated test during a time of abstinence improved after smoking marijuana. (What is unclear is whether this subject may have actually been experiencing cannabis withdrawal from his abstinence, with alleviation of his symptoms through subsequent use of marijuana.[87]) Another small case series[88] showed an improvement in self-injurious behaviors among adolescents following dronabinol therapy, but to date, the study has not been published, leaving protocol details scarce. In sum, none of these studies provide sufficient, high-quality data to suggest that cannabis should be recommended for treatment of ASD or ADHD at this time.

Nonetheless, these data have prompted patient and family groups to advocate for the use of cannabis in children,[89] occasionally even partnering with private, for-profit organizations who may stand to gain financially from such arrangements.[90] This movement is coupled by a possibly increasing willingness of physicians to prescribe cannabis for medicinal purposes.[91] Given the significant adverse health effects of cannabis, these two forces may result in issuing of medical marijuana permits for developmental and behavioral diagnoses for which no data on efficacy, safety or tolerability exist. Even if and when studies on cannabis for developmental and behavioral conditions are conducted, they will likely use formulations of oral dronabinol or cannabidiol, both of which can be administered with a known dose and predictable schedule; at this time, the bulk of medical marijuana is sold in plant form, which results in a highly variable dose of active compound and with less predictable onset of effect based on whether it is inhaled or ingested.

Conclusion

Given the current scarcity of data, cannabis cannot be safely recommended for the treatment of developmental or behavioral disorders at this time. At best, some might consider its use as a last-line therapy when all other conventional therapies have failed.[92,93] As marijuana policy evolves and as the drug becomes more readily available, it is important that practicing clinicians recognize the long-term health and neuropsychiatric consequences of regular use. Although a decades-long public health campaign has showcased the harms of cigarette smoking, similar movements to illustrate the hazards of cannabis use have not been as rigorous or successful. As a result, accurate information on regular cannabis use remains poorly disseminated to patients, families and physicians. Further, there are especially few studies examining neurocognitive and psychiatric outcomes among children and adolescents with developmental or behavioral concerns who are exposed to cannabis, and this remains a critical area for future study. In coming to the decision to use marijuana for medicinal purposes, all parties should be fully aware of the long-term hazards of regular cannabis use,

recognize the lack of evidence on its efficacy in developmental and behavioral conditions, and incorporate this information into a careful risk-benefit analysis.

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Table 1 adapted from Frontiers in Psychiatry, Vol. 4, by KM Lisdahl, ER Gilbart, NE Wright, S Shollenbarger, "Dare to Delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function", doi: 10.3389/fpsyt.2013.00053, copyright 2013. Figure 1 adapted from Proceedings of the National Academy of Science of the United States of America, Vol. 110, by MH Meier, A Caspi, A Ambler, H Harrington, R Houts, RS Keefe, K McDonald, A Ward, R Poulton, TE Moffitt, "Persistent cannabis users show neuropsychological decline from childhood to midlife", pages e2657-2664, copyright 2012. Figures 2a and 2b reprinted from The Lancet, Vol. 370, by TH Moore, S Zammit, A Lingford-Hughes, TR Barnes, PB Jones, M Burke, G Lewis, "Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review", pages 319-328, copyright 2012, with permission from Elsevier."

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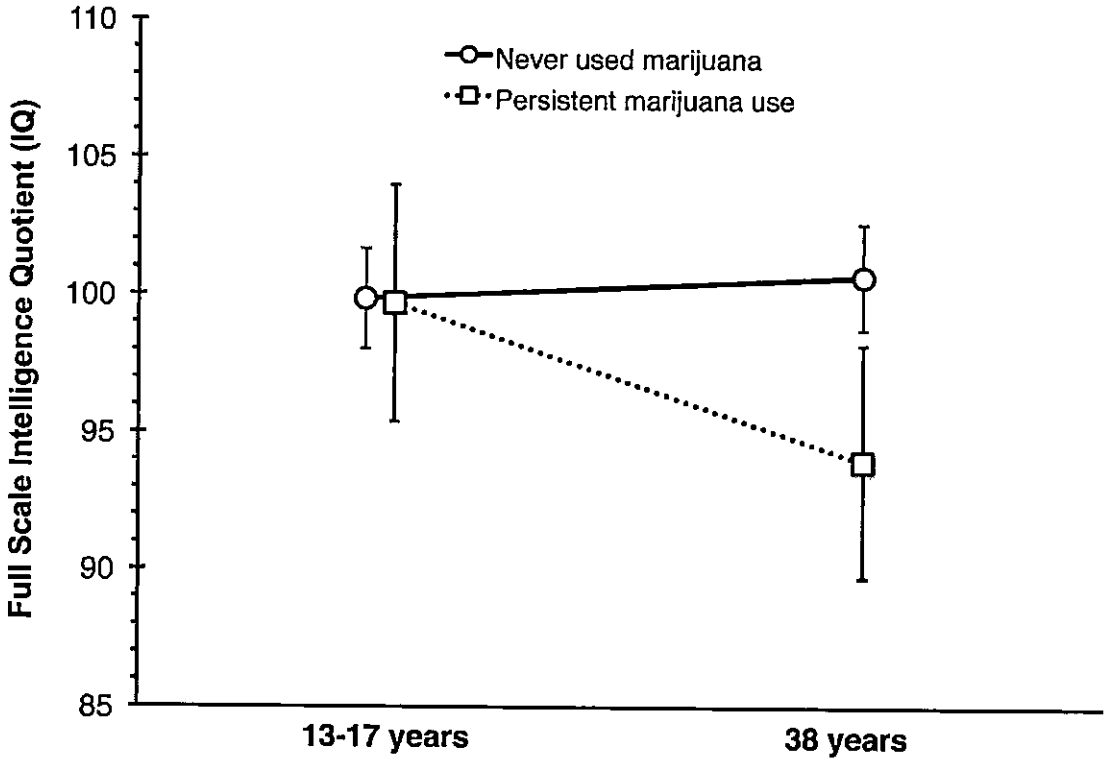

Figure 1.

Full-scale intelligence quotient (IQ) among New Zealanders measured in childhood/adolescence (7-13 years) and adulthood (38 years). This figure highlights findings from 242 individuals who never used cannabis as compared to 38 individuals who demonstrated persistent use during study follow-up. (Persistent use was defined as reporting cannabis use ≥4 times per week at 3 or more study follow-up visits.) Error bars represent ±95% confidence intervals for the estimates. Adapted from Meier *et al.*, 2012.[63]

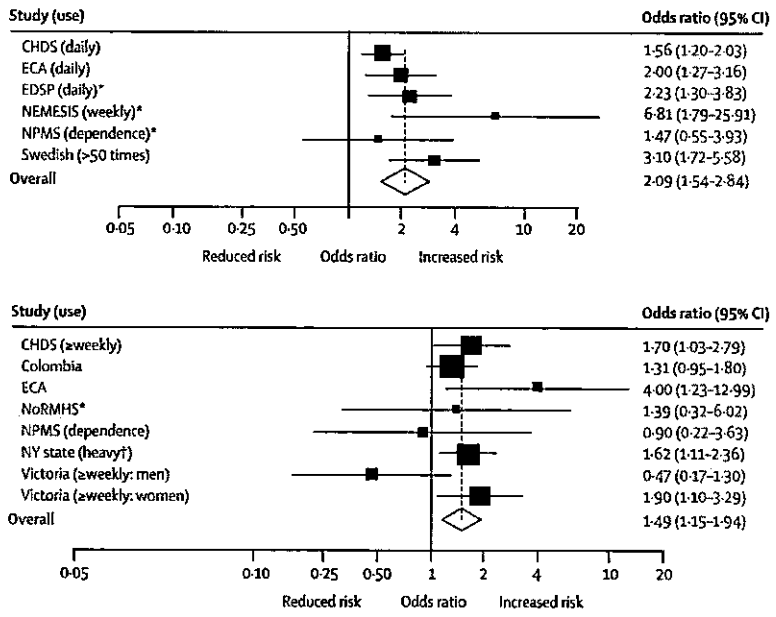

Figure 2.

a: Forest plot reproduced from Moore *et al.*[64] demonstrating adjusted odds ratios and 95% confidence intervals (CI) for association of heavy cannabis use with psychosis. Frequency of cannabis use examined in the study is reported in parentheses. Asterisks denote studies in which results were not adjusted for other drug use. (Reproduced with permission from The Lancet.)

b: Forest plot reproduced from Moore *et al.*[64] demonstrating adjusted odds ratios and 95% confidence intervals (CI) for association of heavy cannabis use with depression. Frequency of cannabis use examined in the study is reported in parentheses. (Reproduced with permission from the Lancet.)

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Table 1

Select studies[a] demonstrating changes in cognition, brain structure and brain function associated with cannabis use in which adolescent onset is associated with worsened outcome.

Reference	Cognitive	Brain Structure	Brain Function
Meier et al., 2012	↓ intelligence quotient (IQ)		
Pope et al., 2003	↓ intelligence quotient (IQ)		
Ehrenreich et al., 1999	↓ attention		
Huestegge et al., 2002	↓ visual search		
Fontes et al., 2011	↓ executive functioning		
Solowij et al., 2012	↓ executive functioning		
Churchwell et al., 2010		↓ prefrontal cortex volume	
Gruber et al., 2011	↑ impulsivity	↓ white matter integrity in prefrontal cortex	
Lopez-Larson et al., 2011		↓ superior prefrontal cortex thickness	
Wilson et al., 2000		↓ total gray matter, ↑ total white matter	
Becker et al., 2010a			↑ left superior prefrontal cortex fMRI[b] blood oxygen level dependent (BOLD) signal during working memory task
Gruber et al., 2012			↓ anterior cingulate fMRI[b] blood oxygen level dependent (BOLD) signal during inhibition task
Jager et al., 2010			↑ prefrontal cortex MRI[b] blood oxygen level dependent (BOLD) signal during novel stimuli presentation in working memory task

[a] Adapted from a larger compilation of studies presented by Lisdahl *et al.*[53]

[b] fMRI denotes functional magnetic resonance imaging.