DEPARTMENT OF HEALTH

Brief Review of Human Studies Regarding Increased Risk of Harm with Cannabis Use

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Introduction

As with any medication, the potential risks with medical cannabis use must be weighed against potential benefits. There are still relatively few clinical trials focused on medical cannabis use, especially large clinical trials that can produce the most definitive results. However, there is a growing body of evidence that certain groups may be particularly susceptible to harm from cannabis use, either because of its impact on the developing brain, or because of the correlation between cannabis use and psychotic disorders such as schizophrenia.

The following groups are believed to be at increased risk of harm from use of cannabis.

- Children, adolescents, and young adults.
- Women who are pregnant or breastfeeding.
- People with a personal or family history of psychotic disorder such as schizophrenia.

People in these groups should generally not use medical cannabis without careful consideration of the risks and benefits for each person's unique situation in consultation with a health care provider. This document provides a brief review of cannabis studies that are relevant to each group described above.

Cannabis Use and Brain Development

Human studies on cannabis use and brain development fall primarily into two categories:

- Measures of structural and functional changes with the brain involving non-invasive brain imaging techniques (see Batalla, Bhattacharyya et al., 2013 for a review).
- Measures of changes in neurocognitive functioning in cannabis users against comparison groups (typically individuals who are similar to study participants but who do not use cannabis) as a potential indirect measure of cannabis-related brain changes.

Recent studies include a growing number of longitudinal studies that have followed patients over time, giving a more complete picture of the longer-term impact of cannabis use.

Evidence shows cannabis use during adolescence is linked to brain changes. However, additional studies are needed to better understand these connections and their impacts.

- Of human brain imaging studies that have found structural differences in young cannabis users, the majority of the evidence points to changes in medial temporal regions (learning and memory, emotional processing) (Ashtari, Avants et al., 2011, Gilman, Kuster et al., 2014), and frontal regions (decision-making, executive and cognitive functioning, response inhibition, emotion regulation, resting functional connectivity (Lopez-Larson, Bogorodzki et al., 2011, Filbey, Aslan et al., 2014, Camchong, Lim et al., 2017, Albaugh, Ottino-Gonzalez et al., 2021, Owens, Albaugh et al., 2022).
- More recent studies also show changes in amygdala reactivity in adolescent cannabis users, which has been shown to predict future cannabis use in a dose-response fashion (Spechler, Chaarani et al., 2020). Similarly, regions of the brain and networks associated with inhibitory functions, affect regulation and reward circuitry (e.g., prefrontal cortex) have been shown to be impacted by THC exposure (Martz, Trucco et al., 2016, Lichenstein, Musselman et al., 2017, Stringfield and Torregrossa 2021). Increased connectivity of reward-related regions of the brain in cannabis-using adolescents may lead to increased addictive behaviors (Nestor, Behan et al., 2020, Subramaniam and Yurgelun-Todd 2020).
- New analysis of adolescent brain imaging studies suggests cannabis use may also impact the superior temporal (responsible for ability to produce sound and process speech) and occipital (responsible for ability to recognize objects) regions of the brain. However, age, gender, and amount of cannabis consumed over the person's lifetime also appear to have an influence. Therefore, more long-term studies are needed (see Allick, Park et al., 2021 for a meta-analysis).
- One longitudinal study of 500 American adolescents showed that exposure to cannabis as an adolescent alters brain-derived neurotropic factor (BDNF), which is critical for brain development and plasticity. The earlier cannabis use was initiated, and the heavier the use over time, the more m-BDNF was produced, leading to alterations in brain function and structure (Miguez, Chan et al., 2019).
- Other studies have also shown no structural differences between young cannabis users and non-users (Block, O'Leary et al., 2000, Delisi, Bertisch et al., 2006, Burggren, Shirazi et al., 2019). For example, one study examined a subset of the Pittsburgh Youth Study which followed boys

ages 13-19 to 30-36. Four categories of cannabis trajectories were identified (non-users/infrequent users, desisters, escalators, and chronic-relatively frequent users). Boys in different trajectory subgroups did not differ on adult brain structure in any subcortical or cortical region of interest (Meier, Schriber et al., 2019).

Evidence is growing that adolescent cannabis use is linked to cognitive declines, but the degree to which cannabis is solely responsible for these changes is unclear.

- There is growing evidence that adolescent cannabis use is particularly associated with poorer attentional processing, executive functioning, and memory (Harvey, Sellman et al., 2007, Fontes, Bolla et al., 2011, Tait, Mackinnon et al., 2011, Gruber, Sagar et al., 2012, Levine, Clemenza et al., 2017, National Academies of Sciences 2017, Mooney-Leber and Gould 2018). It is also linked to poor social and behavioral outcomes later in life, as well as neurocognitive deficits. These effects are often associated with relevant factors including the length and magnitude of exposure (Stringfield and Torregrossa 2021). However, the extent to which these deficits persist following an adequate period of abstinence remains unclear (Scott, Slomiak et al., 2018, Blest-Hopley, Giampietro et al., 2019, Blest-Hopley, O'Neill et al., 2020).
- Despite the association between adolescent cannabis use and cognitive declines, the actual degree to which adolescent cannabis use may be directly or solely related to these declines is uncertain. For example, in one study comparing 40 young adults with cannabis use disorder with 20 healthy controls, those using cannabis consistently performed more poorly with respect to cognitive functions and executive controls. Yet the authors note further research is required to determine whether the poor cognitive performance results in cannabis use, or is a consequence of cannabis (Selamoglu, Langley et al., 2021). This lack of clarity is generally true for case-control studies which cannot decisively determine that cannabis use predates any observable declines in neurocognitive functioning (see Tervo-Clemmens, Simmonds et al., 2018 as an example).
- Educational outcomes related to cannabis use tend to be confounded with the use of other substances, particularly tobacco/smoking cigarettes (National Academies of Sciences 2017).
- Longitudinal studies show both cognitive predictors of cannabis use and cognitive results of cannabis use among adolescents.
- Debenham's 2021 review of longitudinal studies found that aberrant or delayed emotional development predicted higher frequency cannabis use, and deficits in complex attention proceeded cannabis use (and other substances), while deficits in delayed recall, visuospatial function, and executive function followed cannabis use (Debenham, Birrell et al., 2021).
- Other individual longitudinal studies show an impact of cannabis use on inhibitory control, working memory, delayed memory recall (Morin, Afzali et al., 2019), and intelligence (Meier, Caspi et al., 2012).

Earlier cannabis use is associated with a greater risk of developing cannabis dependence later in life.

- There is evidence that adolescent use of cannabis is linked to use of other substances later in life, such as alcohol, tobacco, and other drugs (Timberlake, Haberstick et al., 2007), but most studies are limited by self-reported data on substance use, and recall bias (National Academies

of Sciences 2017). Some links between cannabis and other substance use disappear once early use of alcohol or tobacco, or other confounders, are taken into account. Further, the Colorado Twin Study found that substance use disorders can be predicted by the use of alcohol, tobacco, or cannabis in adolescence, following a model of generalized risk (Palmer, Young et al., 2009).

- The National Academies of Science, Engineering, and Medicine concluded that initiating cannabis at an earlier age is a risk factor for developing cannabis abuse in adulthood (National Academies of Sciences, 2017).

Medical cannabis products have varying levels of THC and CBD, and their use should be carefully considered for youth and young adults.

- Human studies examining cannabis use and brain development primarily focuses on the use of recreational cannabis products, which have relatively high levels of THC, and more recently developed cannabis products have much higher THC concentrations than those examined in earlier studies (Dhein 2020). Minnesota medical cannabis products, on the other hand, have varying ratios of THC to CBD, especially for seizure disorders. For more information, visit the Dosing and Chemical Compositions Report (www.health.state.mn.us/people/cannabis/practitioners/compositionreport.html). The available evidence cannot easily be generalized to all medical cannabis products and should be considered carefully with a health care provider in the context of individual risks and benefits.
- With respect to CBD-dominant products, care should be taken when using CBD-enriched cannabis extracts since extracts still contain THC. It may be safer for children, youth, and young adults to use pure GMP-grade CBD, whether synthetic or plant derived, to avoid possible THC intoxication (Schonhofen, Bristot et al., 2018).

More research is needed.

- Overall, evidence suggests that more research is needed to better understand the cannabis use-brain development relationship, along with greater efforts amongst researchers to standardize on research methodology and definitions to be able to generalize results across studies (Levine, Clemenza et al., 2017). For example, there is inconsistency across studies regarding how levels of cannabis use are measured and described (e.g., “chronic user” or “heavy user”), which makes comparison across studies difficult, and makes it impossible to determine any dose-response outcomes (Morin, Afzali et al., 2019, Fisher, Moore et al., 2021, Lichenstein, Manco et al., 2022).
- Additional research is also needed to understand the impact of medical cannabis on the brain where there may be specific medical conditions and biological variables that confound causal mechanisms and impacts (Burggren, Shirazi et al., 2019).

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Cannabis Use in Pregnancy and Breastfeeding

Data from both animal and human studies suggest that prenatal or perinatal cannabis exposure can result in long-term neurological impairments (Alpar 2016). The American College of Obstetricians and Gynecologists Committee on Obstetric Practice discourages the use of medical cannabis during preconception, pregnancy, and breastfeeding due to concern for potential harm including impaired neurodevelopment (Committee on Obstetric Practice 2015). Studies of cannabis use in pregnancy and breastfeeding have focused on two primary areas:

- Increased risk of adverse pregnancy outcomes, such as preterm delivery, low birth weight or growth issues, and birth defects.
- Increased risk of newborn behavioral issues, as well as long-term cognitive and behavioral functioning.

Six large cohort studies have examined links between prenatal cannabis exposure (PCE) and later impacts on offspring:

- The Ottawa Prenatal Prospective Study (OPPS) by Fried and colleagues (Fried et al., 1998) included 140 cannabis users and 50 controls in the 698 study participants. Cannabis use was categorized into a) no use; b) mild/moderate use up to six joints per week; and c) heavy use of at least six joints per week. Offspring were followed until the ages 18 to 22 years.
- The Maternal Health Practices and Child Development (MHPCD) Study (Day and Richardson, 1991) started in 1982. The study included patients from a Pittsburgh prenatal clinic who used two or more joints per month, and an equal number of controls for a total study population of 564. Prenatal cannabis use was measured by an average number of joints per day for each of the three trimesters of pregnancy. Offspring were followed up to the age of 14.
- The Generation R (GenR) study started in 2001, and included study participants in Rotterdam, the Netherlands from Dutch, Moroccan, Surinamese, and Turkish backgrounds (Jaddoe et al., 2012). Of 9,778 study participants, 220 reported cannabis use in pregnancy, usually in the first trimester (Huizink, 2014). Participants answered questions about substance use three times during pregnancy. The study analyzed results based on whether participants had used cannabis, tobacco, or neither during pregnancy. Offspring are followed through adulthood.
- The Adolescent Brain Cognitive Development Study (ABCD) is a national population-based cohort study of roughly 12,000 young adolescents enrolled between 9 and 10 years from 21 sites across the U.S. Participants are planned to be followed longitudinally for 10 years. Study participants were mostly biological mothers and were asked about the enrolled children's prenatal exposure to cannabis, tobacco, and alcohol.
- The Lifestyle and Early Achievement in Families study (LEAF) is an historical cohort with continued follow-up that assesses the association of in utero marijuana exposure, documented prospectively by biomarker, self-report, and medical records, with executive function and aggression at age 3½-7 years. Women who enrolled in the Perinatal Research Repository during prenatal care at Ohio State University Wexner Medical Center are recontacted for additional follow-up 3 ½ - 7 years post-birth. 362 children are eligible for inclusion.

- The Norwegian Mother and Child Cohort Study (MoBa) is an effort to detect causes of serious diseases through estimation of specific exposure-outcome associations among children as well as their parents. Pregnant women receiving an ultrasound were invited to participate. 95,000 mothers, 75,000 fathers, and more than 114,000 children are included in the cohort. Children were born between October 1999 and July 2009. Blood samples from mothers, fathers, and children as well as DNA, RNA, plasma, and urine samples have been collected, as well as questionnaire responses collected 6 months, 18 months, and 3 years after birth. Additional follow-up is planned.

Generally, conclusions from the evidence are limited by inability to exclude effects of cigarette smoking or other confounders, and unreliable reporting of cannabis exposure due to self-report data and lack of standardization in quantifying exposure. In addition, self-reported prenatal cannabis use has been found to underestimate prevalence measured by positive toxicology by at least 50% (Young-Wolff, Tucker et al., 2017, DiGuiseppi, Crume et al., 2021) in part due to maternal concerns for possible legal consequence, loss of custody, or feelings of guilt associated with substance use while pregnant (Roncero, Valriberas-Herrero et al., 2020).

Cannabis use during pregnancy may be linked to some adverse pregnancy outcomes, but evidence is mixed.

- There is evidence linking PCE to low birth weight (Linn, Schoenbaum et al., 1983, Day, Sambamoorthi et al., 1991, Shaw, Velie et al., 1996, Williams, Correa et al., 2004, Forrester and Merz 2006, van Gelder, Reefhuis et al., 2010, Brown, Mensah et al., 2016, National Academies of Sciences 2017, Metz and Borgelt 2018, Kharbanda, Vazquez-Benitez et al., 2020, Corsi, Murphy et al., 2021, Straub, Mou et al., 2021). However, in several studies the association between prenatal cannabis use and low birth weight disappeared after adjusting for confounders such as tobacco, opioids, or other drugs (see National Academies of Sciences 2017 for a summary of the evidence) including one meta-analysis (Conner, Bedell et al., 2016). Further, MPHCD "found an increase in birth weight in neonates exposed to cannabis during the third trimester of gestation" (Navarrete, Garcia-Gutierrez et al., 2020). In the OPPS study, low birth weight did not persist: offspring with heaviest PCE were lightest at birth but experienced the greatest weight gain after birth, and were heaviest at 1 year (Fried, James et al., 2001). Generation R found "an independent effect of cannabis use" on fetal growth especially when cannabis use by the pregnant mother began early in pregnancy and continued throughout the entire pregnancy" (Navarrete, Garcia-Gutierrez et al., 2020).
- The National Academies of Science, Medicine, and Engineering concluded in 2017 that there is mixed evidence linking PCE to a decrease in birth length although the mechanisms for this link may be more due to smoking and oxygen restriction similar to that observed as a result of smoking tobacco cigarettes than the chemical compounds in cannabis (National Academies of Sciences 2017).
- Some reports show evidence that cannabis use may be associated with increased risk of birth defects including anencephaly, ventricular septal defects, and gastroschisis (Williams, Correa et al., 2004, Forrester and Merz 2006, Forrester and Merz 2007, van Gelder, Reefhuis et al., 2010). At the same time, there are limited reports that have found no significant association between cannabis use and neural tube defects, SIDS or major or minor

malformations (Linn, Schoenbaum et al., 1983, Shaw, Velie et al., 1996, Scragg, Mitchell et al., 2001).

- A few studies report increased risk of preterm delivery (Hayatbakhsh 2012, Dekker 2012, Bada 2005, Saurel-Cubizolles 2014), [(Luke S et al., 2019, Leemaqz SY et al., 2016, Corsi DJ et al., 2019) (all cited in Navarrete, Garcia-Gutierrez et al., 2020)] but others report no association (Day, Sambamoorthi et al., 1991), [(Fergusson 2002, Shiono 1995, de Moraes Barros MC et al., 2006) (cited in Navarrete, Garcia-Gutierrez et al., 2020)], Gunn 2016, cited in Metz) Kharbanda EO et al., 2020. Importantly, most of the studies showing a link between cannabis use and preterm birth were not able to disentangle the confounding effects of tobacco use, which has also been shown to be linked to preterm birth.
- The National Academies of Science, Medicine, and Engineering concluded in 2017 that evidence is insufficient to draw a link between PCE and other adverse pregnancy outcomes (National Academies of Sciences 2017).
- Some studies have implicated cannabis exposure during pregnancy in increased admission to the NICU (Warshak, Regan et al., 2015, Gunn, Rosales et al., 2016, Corsi, Murphy et al., 2021). Other meta-analyses have found no association between cannabis use and NICU admissions (Conner, Bedell et al., 2016, Metz and Borgelt 2018). The National Academies report cautioned that NICU admissions may have more to do with hospital procedures that require NICU admission for newborns of mothers with a history of substance use, rather than differences in birth outcomes or vitality (National Academies of Sciences 2017).

There is some preliminary evidence linking prenatal cannabis exposure (PCE) to fetal brain changes.

- Recent studies have shown PCE linked to brain changes, such as the development of central dopamine and opioid neurotransmitter systems in brain areas regulating reward and motivation, which can impact attention, learning, memory (Navarrete, Garcia-Gutierrez et al., 2020). In particular, the dopamine receptor D2 was decreased in brains exposed to cannabis in-utero (Smith, Kaufman et al., 2020).
- PCE has also been linked to increases in brain connectivity to regions associated with less favorable outcomes and decreased connectivity to regions associated with more favorable outcomes (Thomason, Palopoli et al., 2021).

There is mixed evidence regarding prenatal cannabis exposure (PCE) and early childhood cognitive and behavioral impairment.

- There is mixed evidence on whether cannabis use may be linked to newborn behavior issues (de Moraes Barros 2006, Richardson 1989, Lester 1989).
    - For example, the OPPS study showed that infants with PCE had increased startle response, tremors, and deficient habituation to visual stimuli compared to those without PCE (Fried, Watkinson et al., 1987, Corsi, Murphy et al., 2021).
    - Studies looking at cognitive development from birth to age 3 found no differences between children with PCE and children without PCE (National Academies of Sciences 2017).

- Both OPPS and MHPCD looked at cognitive effects from 36-60 months, and both found a weak effect on short-term memory (National Academies of Sciences 2017).
- One recent study found that PCE negatively impacts fetal brain development and behavioral self-regulation at 1 and 3 months post-birth, but that stopping marijuana use before 10 weeks gestation prevented these effects (Hoffman, Hunter et al., 2020).

There is mixed evidence linking prenatal cannabis exposure (PCE) to cognitive declines in adolescence, young adulthood, and later adulthood.

- A growing number of studies have examined cannabis use during pregnancy and the offspring's long-term cognitive functioning. Deficits in short term memory, impulse control and attention have been consistently associated with PCE (Fried, O'Connell et al., 1992, Leech, Richardson et al., 1999, Goldschmidt, Day et al., 2000, Fried, Watkinson et al., 2003, Goldschmidt, Richardson et al., 2008, El Marroun, Hudziak et al., 2011, Murnan, Keim et al., 2021, Paul, Hatoum et al., 2021). There is moderate evidence from both MHPCDS and OPPS suggesting prenatal cannabis use is linked to impaired response, memory, learning, vocalization, verbal parameters, reading, spelling, and reading comprehension from 4 years to 22 years old (Fried and Watkinson 1990, Day, Richardson et al., 1994, Richardson, Day et al., 1995, Fried, Watkinson et al., 1999, Goldschmidt, Richardson et al., 2008, Willford, Chandler et al., 2010, Goldschmidt, Richardson et al., 2012, Navarrete, Garcia-Gutierrez et al., 2020).
- Other studies, including GenR and ABCD found no differences in cognitive or motor development between children with PCE and those without (Fried and Watkinson 1988, Richardson, Day et al., 1995, El Marroun, Tiemeier et al., 2010, Navarrete, Garcia-Gutierrez et al., 2020).
- The National Academy of Sciences report found insufficient evidence to support or refute an association between maternal marijuana use and later childhood outcomes such as cognition and academic achievement (National Academies of Sciences 2017).
- One later study of 354 adolescents who had been followed since birth identified persistent specific cognitive deficits in adolescents with PCE in perceptual reasoning IQ, a nonverbal executive function that reflects abstract categorical reasoning, after controlling for multiple additional drug and environmental factors related to outcomes. PCE also predicted poorer visual response control on a distractibility task, with higher PCE linked to less ability to sustain effort and stay on tasks presented visually (Singer, Min et al., 2018).

There is growing evidence that prenatal cannabis exposure (PCE) is associated with behavioral problems in adolescence, young adulthood, and later adulthood.

- There is some evidence that cannabis use may be associated with behavioral problems such as attention problems, aggression, hyperactivity, impulsivity, depression, and delinquent behaviors (Goldschmidt, Day et al., 2000, Fried, James et al., 2001, Gray, Day et al., 2005, Noland, Singer et al., 2005, Day, Leech et al., 2011, El Marroun, Hudziak et al., 2011, Jaddoe, van Duijn et al., 2012, Pinky, Bloemer et al., 2019, Paul, Hatoum et al., 2021), especially in girls (Hofman, Jaddoe et al., 2004), although the extent to which the differences persisted over time varied greatly. For example, both OPPS and MHPCD showed increased impulsivity in 9-12 year olds (Fried, Watkinson et al., 1998, Goldschmidt, Day et al., 2000), and the

OPPS cohort showed decreased sustained attention as late as 16 years of age (Fried, Watkinson et al., 2003).

- The ABCD study showed a link between any prenatal cannabis use and sleep-wake disorders among 9- and 10-year-olds (Winiger and Hewitt 2020).
- While many studies have not distinguished links between prenatal cannabis use and tobacco or alcohol use and behavioral outcomes, Cioffredi et al., 2022 used data from the ABCD study and compared 224 nine- and ten-year-olds with PCE to two different matched control groups: one with no prenatal exposure of any kind (n=224), and one with alcohol and tobacco prenatal exposure but no PCE (n=224). The study found similar attentional deficits for PCE, but no neurocognitive differences or brain imaging differences between the three groups (Cioffredi, Anderson et al., 2022). It should be noted there are studies that found no such links once covariates were accounted for (e.g., Fine, Moreau et al., 2019).
- MHPCD, GenR and ABCD cohorts have demonstrated PCE was associated with increased externalizing problems reported on the CBCL in early adolescence. (Goldschmidt, Day et al., 2000, Paul, Hatoum et al., 2021).
- Cannabis may not be the only influence on adverse outcomes; one recent report from the ABCD study showed a cumulative effect of multiple prenatal exposures such as unplanned pregnancy; maternal alcohol, marijuana, and tobacco use early in pregnancy; pregnancy complications; and birth complications on Child Behavior Checklist scores (Roffman, Sipahi et al., 2021).

There is insufficient evidence to link prenatal cannabis exposure (PCE) to substance use later in life.

- While some studies have identified a correlation between PCE and both tobacco smoking and cannabis use later in life (National Academies of Sciences 2017, Pinky, Bloemer et al., 2019), it is extremely difficult to tease out the impact of PCE from socio-economic status, home life environment, and other confounding factors (National Academies of Sciences 2017).

Prenatal cannabis exposure (PCE) has been linked to small increases in the risk for psychopathology later in life.

- Several studies have shown PCE after maternal knowledge of pregnancy to be associated with small increase in the risk for psychotic-like experiences during middle childhood, even after accounting for potentially confounding variables (Bolhuis, Kushner et al., 2018, Navarrete, Garcia-Gutierrez et al., 2020, Corsi, Murphy et al., 2021, Paul, Hatoum et al., 2021).
- Fine et al., 2019 showed similar findings for PCE after knowledge of pregnancy both with and without covariates. However, for PCE before knowledge of pregnancy, the same study found no increase in psychosis proneness once covariates were included in the model (Fine, Moreau et al., 2019).

There is insufficient evidence to link maternal cannabis use while breastfeeding to any changes in offspring.

- Evidence on harms associated with cannabis use while breastfeeding is extremely limited. Perez-Reyes et al., report that THC was detected in the breast milk of two women using cannabis (Perez-Reyes and Wall 1982). In another study, cannabinoids were detectable in 34 (63%) of the 54 analyzed samples, up to 6 days after the last reported use (Bertrand, Hanan et al., 2018).
- Findings are mixed on whether cannabis use during breastfeeding is associated with poorer motor development in infants (Tennes, Avitable et al., 1985, Astley and Little 1990).
- It is relatively rare for women to start using cannabis exclusively after a child is born. Therefore, it is extremely difficult to tease out the impact of maternal cannabis use while breastfeeding from the impact of PCE (Corsi, Murphy et al., 2021).

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Cannabis Use and Psychotic Disorders

Studies have reported prevalence of cannabis use among people experiencing first episode psychosis of one-third to two-thirds of patients (Barbeito, Vega et al., 2013, Colizzi, Carra et al., 2016, Toll, Berge et al., 2020). Similarly, people who use or abuse substances (including cannabis) can sometimes (National Academies of Sciences 2017). In 2014, nearly 8 million U.S. adults reported co-occurring substance abuse and mental health disorders (National Academies of Sciences 2017). There are three primary theories for the reasons behind this co-occurrence:

- Substance use may increase the risk of developing a mental health disorder by changing brain structure and chemistry in ways that impact mental health.
- Mental illness may increase the risk of developing a substance use disorder insofar as people experiencing subclinical symptoms of mental illness may be more likely to self-medicate with drugs, including cannabis.
- Several types of risk factors including genetics, environment, early childhood trauma, etc. may contribute to the development of both substance abuse and mental health disorders.

Research on cannabis and psychotic disorders can be grouped into two categories: 1) the relationship between cannabis use and the onset of psychotic disorders, and 2) the impact of cannabis use on people already exhibiting psychotic symptoms or diagnosed with a psychotic disorder.

Cannabis use and onset of psychotic disorders

Evidence exists that cannabis contributes to the onset of psychotic disorders, especially among people already at risk for developing a psychotic disorder.

- Recent review articles concur there is strong evidence of a causal role for cannabis use, especially for persons already at increased risk for developing a psychotic disorder due to genetics, history of child mistreatment, or other reasons (Burns 2013, Radhakrishnan, Wilkinson et al., 2014, Manseau and Goff 2015, Ortiz-Medina, Perea et al., 2018, Carlyle, Constable et al., 2021, Wainberg, Jacobs et al., 2021), though some note a causal role cannot be fully concluded from existing evidence. Some argue cannabis use could be a component cause that interacts with genetic and environmental factors in vulnerable populations (Moore, Zammit et al., 2007, Manseau and Goff 2015, Johnson, Hatoum et al., 2021) or that other mediational factors need to be taken into account (Fonseca-Pedrero, Lucas-Molina et al., 2020). Many point to the need for additional research (see Alvarez, Gomar et al., 2019 as an example).
- The National Academies of Sciences conducted a review of the evidence in 2017, and found that cannabis use is likely to increase the risk of developing schizophrenia and other psychoses (National Academies of Sciences 2017). Further, younger initiation of cannabis, as well as more frequent and higher dose of cannabis used, increased the risk of psychosis (Marconi, Di Forti et al., 2016, National Academies of Sciences 2017, Stilo and Murray 2019, Wright, Cather et al., 2021). The National Academies report found the association between cannabis use and development of a psychotic disorder to be moderate to large, but noted it may be moderated by genetic factors.

Cannabis use lowers the age of onset of first psychosis.

- A meta-analysis of 83 studies found that age of onset of psychosis for cannabis users was 2.7 years younger than for non-users (Large, Sharma et al., 2011). The authors note that even if the effect of cannabis use is to move forward by a few years the time of schizophrenia onset for persons destined to develop the disease, the impact of the change in time of onset could be large. Onset of schizophrenia often occurs in late adolescence or early adulthood, a time at which a delay of a few years could allow many patients to achieve important developmental milestones of late adolescence and early adulthood that could reduce long-term disability resulting from the disorder.
- Similar findings were observed in a study of 331 patients with cannabis-induced psychosis (n=69), schizophrenia with cannabis use or abuse (n=57), and schizophrenia with no use or abuse of cannabis or other drugs, excluding tobacco (n=181). The average age of first hospital admission due to psychosis was lower for the two cannabis-using groups (26.1 for cannabis-induced psychosis group; 25.3 for those with schizophrenia and cannabis use; and 31.1 for those with schizophrenia and no cannabis use, $p<.001$) (Rentero, Arias et al., 2021).

Recent studies suggest that THC may be primarily involved in triggering psychotic episodes, but more research is needed, especially related to medical cannabis use.

- THC is clearly recognized to be the cause of psychotic effects (D'Souza, Perry et al., 2004) and use of higher THC products has been shown to be more strongly associated with development of psychotic disease than use of lower THC cannabis (Di Forti, Marconi et al., 2015). Results of two longitudinal studies published in 2015, as well as the EU-GEI study, suggest caution in considering cannabis, in general, a cause of psychotic disease and highlight the role of high THC cannabis as a causal agent.
  - Pittsburgh Youth Study data was used to characterize trajectories of marijuana use from age 14 to age 36 among 506 participants: 1) low/non-users (46%), late-increasing (21%), adolescent limited (11%), and early-onset chronic (22%). The authors found no difference in diagnosed psychotic disease among the four groups (Bechtold, Simpson et al., 2015).
  - A study of 461 patients hospitalized for the first time with a psychotic disorder in South London and a control group found a three-to-five-fold increase in odds of first-episode psychosis among persons using high-THC marijuana and no increase in risk among patients smoking low-THC marijuana (Di Forti, Marconi et al., 2015).
  - The EU-GEI study examined frequency of daily cannabis use and use of high-potency cannabis and their relationship to the incidence of psychotic disorder in 11 sites in Europe. The study has found that if high-potency cannabis was no longer available, around 12% of first-episode psychosis cases across 11 Europe-wide sites could be prevented, rising to 30% in London and 50% in Amsterdam (Di Forti, Quattrone et al., 2019). See the European network of national schizophrenia networks studying gene-environment interactions (https://www.eu-gei.eu/).
- There is growing evidence that CBD has anti-psychotic effects (see Schubart, Sommer et al., 2014 for a comprehensive review of animal, clinical, and epidemiological evidence) (see Iseger and Bossong 2015 for a review of studies on human subjects). At least one clinical

trial has been carried out on CBD as an antipsychotic agent (Leweke, Piomelli et al., 2012). Though its strength is limited by small sample size (n=42), the study found no significant difference in effectiveness between treatment with CBD versus amilsulpride for patients with acutely exacerbated schizophrenia. However, CBD displayed a much better side effect profile.

- The role of CBD in conjunction with THC is still unclear. CBD may attenuate psychotic or memory-impairing effects of THC as reported in one small randomized, double-blind, placebo-controlled, counterbalanced study (n=28) (Ganesh, Cortes-Briones et al., 2022). However, in one small study of cannabis users, a 2:1 ratio of CBD:THC did not show an attenuation of these effects (Morgan, Freeman et al., 2018). Further, in one meta-analysis including 15 studies on THC administration, and 4 studies examining THC plus CBD administration, results showed a single THC administration induced psychotic, negative, and other psychiatric symptoms with large effect sizes. The authors found no consistent evidence that CBD induced symptoms or moderated the effects of THC. These findings highlight the potential risks associated with the use of cannabis and other cannabinoids that contain THC for recreational or therapeutic purposes. They also suggest that simply adding CBD to a THC-dominant product may not reduce the risk of developing psychotic symptoms (Hindley, Beck et al., 2020).
- It should be noted that the relatively large literature on associations between cannabis use and psychotic disease draws nearly exclusively on use of recreational cannabis products, which have relatively high levels of THC. Products accessed through the Minnesota Medical Cannabis Program, on the other hand, have varying ratios of THC to CBD. Existing evidence might very well not apply to patients using medical cannabis products whose CBD content approaches or surpasses its THC content.

Cannabis use in persons with psychotic disorders

Evidence suggests that cannabis has a complex and bi-directional relationship with psychotic symptoms.

- Studies consistently show use of cannabis to be associated with increased relapse or re-hospitalization, and decreased treatment adherence (Zammit, Moore et al., 2008, Stilo and Murray 2019, Scheffler, Phahladira et al., 2021).
- Many studies show use of cannabis to be associated with more severe psychotic symptoms (Stilo and Murray 2019, Ricci, Ceci et al., 2021), although the relationship appears to be bi-directional (see Foti, Kotov et al., 2010). Other studies continue to show no relationship between cannabis use and psychotic symptom severity (Scheffler, Phahladira et al., 2021), and others conclude that cannabis use is not a causal factor in between-group differences for symptom severity (Pope, Manseau et al., 2021). It is important to note which studies account for baseline illness severity, as well as use of alcohol, tobacco, or other drugs.
    - In a longitudinal study (Foti, Kotov et al., 2010)[OB] a group of 229 patients with a schizophrenia spectrum disorder were assessed five times: at first admission for the disorder and 6 months, 2 years, and 10 years later. Across the 10-year follow-up, rates of current cannabis use ranged from 10-18% and use was found to be associated with

more severe psychotic symptoms even after adjusting for severity of symptoms at baseline, adherence to anti-psychotic medications, and use of alcohol and other drugs. From the results of their analytic models the authors concluded the association between cannabis use and psychotic symptoms was bi-directional: changes in cannabis use were predictive of changes in psychotic symptoms and vice versa. Disorganized, depressive, and negative (blunted affect, lack of spontaneity, emotional withdrawal) symptoms were not significantly associated with use.

- A second longitudinal study examined the impact of cannabis use on baseline symptom severity and treatment outcomes in 98 patients with first-episode schizophrenia spectrum disorders. Study participants were treated with a long-acting injectable antipsychotic over 24 months. Results compared current/recent cannabis users with non-users, and suggested that cannabis users and non-users did not differ regarding symptom reduction (Scheffler, Phahladira et al., 2021).
- One observational study examined 247 patients hospitalized with first-episode psychosis between 2008 and 2013 (Pope, Manseau et al., 2021). Cannabis use in the three months prior to hospitalization was assessed. Results showed that those who had used cannabis in the 3 months prior had "less anhedonia and asociality and greater delusion severity." However, the amount or "dosage" of cannabis used in the past three months had no impact on any of the variables examined. The authors suggest that first-episode psychosis patients who use cannabis are different from those who do not, while arguing against the explanation that cannabis use itself has an impact on these variables, since there was no dose-response relationship observed.

Evidence is mixed regarding the impact of cannabis use on cognitive functioning among people with schizophrenia or other psychotic disorder.

- Cannabis was not associated with a difference in cognition/cognitive functioning in a sample of 152 individuals with FEP (first episode psychosis) one year after the psychotic episode (Karpov, Lindgren et al., 2021).
- Heavier doses of cannabis may impact cognitive functioning more severely. One study showed that among first-episode psychosis patients, heavy cannabis users (3+ joints per day) performed more poorly than medium cannabis users (1-3 joints per day) on verbal memory tasks, as well as other neurocognitive tasks (Nunez, Ochoa et al., 2016).
- The National Academy of Sciences reviewed the findings from 14 of the most recent, good- to fair-quality systematic reviews and from 31 primary literature articles that best address the committee's research questions of interest (National Academies of Sciences 2017). Its findings included:
  - In individuals with schizophrenia and other psychoses, a history of cannabis use may be linked to better performance on learning and memory tasks.
  - For individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to greater symptoms of bipolar disorder than for nonusers.

Cannabis use may be associated with an increased risk of violent behavior in people with psychotic disorders.

- In a study of 265 adults 18-35 with first onset psychosis, early onset cannabis use (before age 15) was shown to be predictive of later violent behavior (odds ratio 4.47) when the model was adjusted for age group, other types of substance use, being a user or a nonuser and various violence risk factors and covariates (Moulin, Alameda et al., 2020).
- Data combined from two studies included 1,792 individuals with psychotic disorders. Results showed a greater risk for violent behavior among those who had used any type of substance daily or non-daily (compared to no use) (substances examined included cannabis, stimulants, depressants, and hallucinogens) after controlling for age, sex, and educational level. The pooled odds ratio of violent behavior for daily cannabis use was 1.6, (95% confidence interval 1.2-2.0) (Lamsma, Cahn et al., 2020).

Cannabis abstinence or reduction is associated with improvement in psychotic symptoms.

- Two studies from the United Kingdom with similar methodologies assessed cannabis-using patients with new onset psychosis (Barrowclough, Gregg et al., 2015) and with psychotic disorders of longer duration (Barrowclough, Emsley et al., 2013) at baseline, 12-months and 24-months. In both studies, reduced use of cannabis was associated with better psychological function and, in the first-episode psychosis group, with decreased anxiety, after adjustment for numerous demographic factors and use of alcohol and other drugs. No association was found between continued cannabis use and negative or positive (hallucinations, hearing voices, bizarre ideas) psychotic symptoms.
- Spanish patients with new-onset psychotic disease were studied at baseline and years 1, 3, 5, and 8. Patients who were using cannabis at baseline but discontinued use during follow-up exhibited better psychological functioning and fewer negative symptoms than patients with continued cannabis use, after adjusting for demographics and use of alcohol and other drugs. A trend toward an increase in positive symptoms in the continued use group did not reach statistical significance. The differences between groups became larger after 3 years (Gonzalez-Pinto, Alberich et al., 2011).

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