Minnesota Department of Health
OFFICE OF MEDICAL CANNABIS

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

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
- Persons with a personal or family history of psychotic disorder such as schizophrenia

Persons in these groups should generally not use medical cannabis. A brief review of cannabis studies that are relevant to each group described above has been summarized below.

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CANNABIS USE AND BRAIN DEVELOPMENT

Providing access to medical cannabis for children, adolescents and young adults should be considered carefully based on the current available evidence on cannabis exposure and brain development. While animal studies do show evidence of cannabinoids changing the trajectory of brain development in adolescence (Quinn et al., 2008; Rubino et al., 2009; Schneider & Koch, 2003), human studies are more divided on the matter. Generally speaking, human studies on this topic are divided into two broad categories of evidence. First, studies involving measures of structural and functional changes within the brain have been conducted on humans which typically involve non-invasive brain imaging techniques (see Batalla et al. 2013 for review). Second, studies have examined for changes in neurocognitive functioning in cannabis users against comparator groups (typically non-using controls) as a potential indirect measure of cannabis-related brain changes.

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 et al, 2011, Gilman et al., 2014), and frontal regions (decision-making, executive functioning, response inhibition, emotion regulation; Filbey et al., 2014; Lopez-Larson et al., 2011). However, other studies have also shown no structural differences between young cannabis users and non-users (Block et al., 2000; DeLisi et al., 2006). Studies measuring neurocognitive functioning in adolescents are also divided on the cannabis-brain development relationship. For example, while there is building evidence that adolescent cannabis use is particularly associated with poorer attentional processing, executive functioning, and memory (Fontes et al., 2011, Gruber et al., 2012, Harvey et al., 2007; Tait et al., 2011), the actual degree to which adolescent cannabis use may be directly related to these declines is uncertain. This is generally true for case-control studies which cannot decisively determine that cannabis use predates any observable declines in neurocognitive functioning.

Even with longitudinal research on this particular topic – which can more clearly elucidate on the temporal order of the cannabis-brain development relationship – is mixed on results. In the seminal Meier et al. (2012) longitudinal study, the authors reported on intelligence measures and cannabis use measures that spanned nearly 3-decades. Of most importance, Meier et al. was able to measure intelligence in early adolescence (age 13) in this longitudinal sample (predating the participants' cannabis involvement) and observe for any changes in intelligence by age 38. More frequent cannabis use, as well as more frequent reports of cannabis dependence, both predicted declines in IQ by age 38. In contrast, while evidence from a more recent longitudinal study did find a relationship between cannabis use and some measures of IQ, this relationship did not hold when the authors implemented a cotwin comparator design (Jackson et al., 2016), which effectively controlled for any genetic variations to explain the results. In particular, identical twin pairs that were discordant on cannabis use showed similar changes across time in IQ measures effectively demonstrating that cannabis use may not directly cause declines in IQ. 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 to be able to generalize results across studies.

Lastly, it should be noted that the evidence presented here primarily focuses on the use of recreational cannabis products which have relatively high levels of THC. MN medical cannabis products, on the other hand, have varying ratios of THC to CBD. The ability for the evidence to speak to patients on higher CBD ratio products is even less clear. It is also important to keep in mind that some patients who will enroll in MN's medical cannabis program have qualified due to conditions that heavily rely on central nervous system dysfunction (e.g., seizures). Any changes in brain development/function over time will be confounded by the very nature of their medical conditions.

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CANNABIS USE IN PREGNANCY AND BREASTFEEDING

Animal models have shown that tetrahydrocannabinol (THC) crosses the placenta and results in fetal THC plasma levels approximately 10% of maternal levels after acute exposure; repeat exposure can result in much higher fetal concentrations (Committee on Obstetric Practice 2015). 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). There is evidence suggesting cannabis use during pregnancy may be linked to adverse pregnancy outcomes, preterm delivery, low birth weight or growth issues, birth defects, newborn behavioral issues as well as long-term cognitive and behavioral functioning. The State of Colorado compiled a comprehensive review of harms related to cannabis use during pregnancy and lactation (Colorado Report, 2014); the following includes summaries of a selection of the evidence reviewed in this report, along with results of other reviews. Generally, conclusions from the evidence are limited by sample sizes, 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 (Colorado Report, 2014).

Limited evidence suggests that cannabis use is associated with greater odds of stillbirth (Varner 2014). Other reports show evidence that cannabis use may be associated with increased risk of birth defects including anencephaly, ventricular septal defects and gastroschisis (van Gelder 2009, Williams 2004, Forrester 2007 and 2006). There also exist limited reports which have found no significant association between cannabis use and neural tube defects, SIDS or major or minor malformations (Shaw 1996, Suarez 2007, Linn 1983, Scragg).

Some studies report links between prenatal cannabis exposure and decreased fetal weight in late pregnancy and decreased birth length and weight (van Gelder 2010, Shaw 1996, Suarez 2007, Forrester 2006, Williams 2004, Linn 1983, Day 1991, Brown 2016). A review by Alharbi et al found that studies showed an almost-significant association between cannabis use during pregnancy and mean birth weight, after adjustment for confounders (Alharbi 2014). A few studies report increased risk of preterm delivery (Hayatbakhsh 2012, Dekker 2012, Bada 2005, Saurel-Cubizolles 2014) but others report no association (Day 1991, Fergusson 2002, Shiono 1995). Evidence that cannabis use is associated with low birth weight and small size for gestational age is similarly mixed: in some cases, the increased risk attributed to cannabis use disappeared after adjustment for confounders (Day 1991, Hayatbakhsh 2012, Schempf 2008, Bada 2005, Shiono 1995, Saurel-Cubizolles 2014). There are also a few reports that cannabis use may be linked to decreased height and small size with disproportionate effects on female children (Cornelius 2002, Fried 1999).

Much of the concern around medical cannabis use during pregnancy centers on 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). A small

number of studies examine cannabis use during pregnancy and the offspring's long term cognitive functioning. There is moderate evidence drawing on two large longitudinal cohorts, the Maternal Health Practices and Child Development Study (MHPCDS) in Pittsburgh and the Ottawa Prenatal Prospective Study (OPPS), suggesting prenatal cannabis use is linked to lower IQ scores and decreased cognitive functioning later in life (Day 1994, Goldschmidt 2008, Willford 2010, Fried 1999). There is also some evidence that cannabis use may be associated with behavioral problems such as attention problems, aggression, hyperactivity, impulsivity, depression and delinquent behaviors (El Marroun 2011, Goldschmidt 2000, Fried 2001, Gray 2005, Noland 2005, Day 2011).

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 1982). Findings are mixed on whether cannabis use during breastfeeding is associated with poorer motor development in infants (Astley 1990, Tennes 1985).

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CANNABIS USE AND PSYCHOTIC DISORDERS

Cannabis Use in Persons with Psychotic Disorders

A 2008 systematic review of the impact of cannabis use on patients with established psychotic disorders included 13 longitudinal studies (Zammit 2008). Use of cannabis was associated with increased relapse or re-hospitalization and with decreased treatment adherence fairly consistently across the studies; associations between cannabis use and psychotic symptoms or other psychopathology scores were more inconsistent. Importantly, the authors concluded that confidence most associations reported were specifically due to cannabis was low. Only 4 of the 13 studies made any attempt to adjust for baseline illness severity measures and 8 included no adjustment for use of alcohol and other drugs. Although some adjustment for confounding was undertaken in a number of the studies, only 3 presented both crude and adjusted estimates that enable readers to gauge the potential impact of confounding in the studies. When presented, estimates were attenuated between 15% and 80% even though only a limited number of potentially important confounders were adjusted for in these studies.

More recent longitudinal studies have adjusted for potential confounders more completely, providing additional insight and confidence in the meaning of associations. In one of them (Foti 2010) 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.

Two studies from the UK with similar methodologies assessed cannabis-using patients with new onset psychosis (Barrowclough 2015) and with psychotic disorders of longer duration (Barrowclough 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 (Gonzalez-Pinto 2011). 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 increase in positive symptoms in the continued use group did not reach statistical significance. The differences between groups became larger after 3 years.

Cannabis Use and Onset of Psychotic Disorder

It is a sign that a field of inquiry lacks a clear answer when an article is published that provides an overview of systematic reviews on the topic. Such an overview article on reviews of the association between cannabis use and psychosis was published in 2010, finding five reviews that met its inclusion criteria. Only two of the five were judged to be of good methodologic quality and the other 3 were found to be of poor quality (Minozzi 2010). All five of the reviews draw the conclusion that cannabis is neither a necessary nor a sufficient cause of psychosis but that it could be a component cause that interacts with genetic and environmental factors in vulnerable individuals. One of the two reviews judged to be of high methodologic quality provided both a systematic review and meta-analysis (Moore 2007). It is cited often in the literature as demonstrating cannabis increases risk of developing psychotic disorder. After adjusting for a comprehensive list of potential confounders, any use of cannabis resulted in an odds ratio of 1.41 (95% CI 1.00-1.55) and odds ratio of 2.09 (1.54-2.84) among those who use cannabis most frequently. The other review Minozzi et al judged high quality did not perform a meta-analysis and concluded the causal nature of the association was unclear because of methodological problems in the primary studies. It points out the particular challenge of ascertaining early sub-clinical disease in order to deal with the "reverse causality" hypothesis – that is, the belief that discomfort caused by early symptoms of psychotic disease draws some persons to use of marijuana for relief.

More 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 genetics, history of child mistreatment, or other reasons (Burns 2013, Radhakrishnan 2014, Manseau 2015), though some note a causal role cannot be fully concluded from existing evidence (Manseau 2015). 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 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.

Results of two longitudinal studies published in 2015 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%) (Bechtold 2015). The authors found no difference in diagnosed psychotic disease among the four groups. 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 2015).

Few studies of the association between cannabis use and psychosis have been able to characterize the cannabis used by participants – in particular the THC and CBD content. In all likelihood the THC and CBD content among participants varied considerably. Lack of information on the THC and CBD content adds complexity to interpreting the study results, as it is becoming increasingly evident that the two cannabinoids have very different impacts on psychosis. THC is clearly recognized to be the cause of psychotic effects (D'Souza 2004) and use of higher TCH products has been shown to be more strongly associated with development of psychotic disease than use of lower THC cannabis (Di Forti 2015). But there is growing evidence that CBD has anti-psychotic effects (see Shubart 2014 for a comprehensive review of animal, clinical and epidemiological evidence and Iseger 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 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 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 MN 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.

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