Author: Candice E. Crocker, PhD.

Prepared for CCSA

March 2018

Evidence Review

(to support update to cannabis and psychosis website)

Target population: Youth who are using or considering using cannabis.

Target condition: Negative impacts of cannabis use on mental health; in particular, psychosis.

Methodology: Comprehensive review of the literature in Pubmed (National Library of Medicine) and Web of Science (Clarivate Analytics) around each question with weighting of literature found based on the grade of evidence. The focus was on locating systematic reviews and larger cohort studies from 2011 onward with a focus on the previous 3 years that were open access to allow for links on the website that could be accessed by any interested individual.

Overview

Research has shown that regular cannabis use impacts both psychosis development and the course of psychotic illness. Psychosis is a break with reality characterized by hallucinations, false beliefs (delusions), impaired thinking and what is called negative symptoms that include lack of motivation, lack of energy, and decreased thought processes. Importantly, a psychotic illness can have significant effects on an individual's overall functioning. Cannabis use can cause a temporary psychotic episode in susceptible individuals. Unfortunately, those who have had a "bad trip" on cannabis are at high risk for later development of a psychotic disorder (Shah et al., 2017, Starzer et al., 2017). Regular cannabis use can also impact the development of a

more chronic life-long psychotic disorder in at risk individuals and is associated with an earlier age of onset of psychosis. However, there is currently no way to clearly identify who is at risk of developing psychosis with cannabis use. Regular cannabis use after development of a psychotic illness worsens symptoms and long term outcomes. We now have substantial evidence for a link between cannabis use in adolescence and development of psychosis later in life (National Academies of Sciences and Medicine, 2017). Based on focus groups performed as part of a media campaign (weedmyths.ca) developed by the Nova Scotia Early Psychosis Program (NSEPP), this update was designed as a serious of questions, as one of the themes from the focus group of 15 year olds was that they did not want to be 'preached to' or told what to do. Examples of these questions are quoted in this evidence review.

Effect on the developing brain:

"So, you may be asking why does cannabis use affect mental health especially when use starts as a teenager?" Our current understanding of how cannabis impacts the development of psychosis is linked to the role that cannabis receptors play in brain development (Crocker and Tibbo, 2015). The human brain develops from birth up to about age 25 with maturity being achieved a bit earlier in females than males which is directly related to an earlier onset of puberty in females in general (Herting et al., 2014). The prefrontal cortex is among the last regions to mature. The sequence of brain development is important for timing of the incidence of psychosis as this brain region is most involved in personality, decision making and social behavior. In the developing brain, endocannabinoid receptors (CBR) are used to form correct neuronal connections (Jacobus and Tapert, 2014). Plant cannabinoids such as THC and CBD bind to CBRs and research suggests that the large amount of signal that comes from inhaling or ingesting cannabis overwhelms the normal brain development process (Lu and Mackie, 2016, Crocker and Tibbo, 2015). Synthetic cannabinoids may be significantly worse based on new preclinical work showing they may permanently alter the expression pattern of dopamine receptors as well (Aguilar et al., 2018). The reason adults over 25 are not at the same risk as

adolescents is that these cannabinoid receptors change their expression pattern at the end of brain development from primarily expression on white matter to primarily expression on grey matter (Crocker and Tibbo, 2015, Lu and Mackie, 2016). Endocannabinoids continue to play a role in neurogenesis; however, as CBR and particularly CB_1 receptors also act as a neurogenic niche and this role of supporting brain stem cells is maintained in adults (Diaz-Alonso et al., 2012, Rodrigues et al., 2017).

Association with psychosis onset:

"So how do we know that cannabis use is associated with an increased risk for the development of psychosis?" The association of psychosis development with cannabis use is based on epidemiological studies examining cannabis use particularly in adolescence and later in life psychiatric profiles in the same individuals, that encompass outcomes for hundreds of thousands of people (Malone et al., 2010). Some of the reports stand out for their design such as the first large epidemiological study in a group of 45, 570 Swedish conscripts in 1987 (Andreasson et al., 1987) to a study in 2002 that studied over 4000 individuals who were confirmed psychosis-free and measured whether they used cannabis; then these researchers followed these study subjects for years. This group found that cannabis use increases the risk of developing a psychotic disorder in individuals who were psychosis-free (van Os et al., 2002). Further studies have been done all showing the same outcome, cannabis use in adolescence increases the possibility of developing a psychotic disorder. There is high grade epidemiological evidence in the literature now, so fewer studies of this nature are being conducted, however a recent meta-analysis also confirms this association with the level of cannabis use and development of psychosis (Marconi et al., 2016). Even when prodromal symptoms are adjusted for, there is still an association of cannabis use with psychosis development with a threshold of 5 or more lifetime uses (Mustonen et al., 2018). All of this high grade evidence led the National academies of Sciences and Engineering in the US to label the

association of cannabis use with psychosis development as the only medical effect of cannabis to be supported by substantial evidence (National Academies of Sciences and Medicine, 2017).

Risk factors and Impact on age of onset of psychosis:

"So, what do we know about risk factors for development of psychotic disorders with cannabis use?" The risk of psychosis development with cannabis use varies from an estimated 4x to 12x depending on factors such as family history of mental illness, age at which cannabis use starts and THC content of the cannabis (National Academies of Sciences and Medicine, 2017). Other risk factors that may add to the developmental risk in combination with cannabis use are trauma, migration status, and urbanicity but the interactions are less clear. When these factors are controlled for cannabis use is still a contributing factor to the development of psychosis on its own (Løberg et al., 2014, Henquet et al., 2005). There is currently no way to identify who is at risk of developing psychosis with cannabis use either as a single episode or a full psychotic disorder. To date only a few risk factors have been identified. Some studies show an association with risk of psychosis development being increased by having a first degree relative with a mental illness (Bhatia et al., 2016, Proal et al., 2014). The age at which cannabis use is started another factor. People who use regular cannabis in their early teenage years (<age 15) are at greater risk of developing psychosis and at a younger age. The threshold of use that needs to be exceeded to be at risk is unclear as neuroimaging work has shown effects of cannabis use on brain structure with non-regular recreational use (Gilman et al., 2014, Orr et al., 2016) Meta-analyses have confirmed a relationship between the use of cannabis and an earlier onset of schizophrenia spectrum psychotic disorders; these studies conclude that this widely found association is unlikely to be due to variations in the study methods used or poor quality of studies (Large et al., 2011, Myles et al., 2016). This has recently been further supported by another large naturalistic study which found the only factor associated with earlier onset of psychosis was cannabis use (Helle et al., 2016). The earliest onset is associated with another

risk factor which is higher THC content cannabis strains (e.g. 'skunk'); an average of 6 years earlier onset (Di Forti et al., 2014). This association is so strong that it may be to blame for London, England having one of the highest rates of psychosis incidence in the world (Di Forti et al., 2015). Additionally, high THC, low CBD strains are also thought to be risky (Fischer et al., 2017). A recent study also shows an association between early age of starting tobacco smoking and early use of cannabis, and a more rapid escalation of use in people who go on to develop a psychotic disorder (Pauselli et al., 2018). Overall, this knowledge has led to the development of lower risk cannabis use guidelines that strongly suggest starting cannabis use later in life (Fischer et al., 2017).

The interplay between a psychotic break and a bad trip:

"How can you know if you're experiencing psychosis or just a bad high?" This is a challenging point to explain to individuals who are less aware of what psychosis is. A "bad trip" from cannabis use has some of the same symptoms as a psychotic break. Cannabis use can cause a temporary psychotic episode in some people. Unfortunately, individuals who have experienced a bad trip or drug-induced psychotic episode associated with cannabis are at higher risk for developing a psychotic disorder. Recently published work suggests that having a bad trip on cannabis is more directly associated with developing schizophrenia or bipolar disorder than other illicit substances; 47.4% of those who experience drug induced psychosis with cannabis (95% CI=42.7–52.3) convert to either schizophrenia or bipolar disorder (Starzer et al., 2017). Interestingly, the conversion to schizophrenia was within 3 years while the bipolar conversion occurred within an average of 4.4 years (Starzer et al., 2017) There is also recent encouraging data showing complete abstinence after a single first bad trip (substance induced psychosis) resulted in no further psychiatric conditions (Shah et al., 2017). Additionally, there may be a linkage between individuals experiencing greater psychotic experiences with cannabis use having a greater likelihood for cessation of cannabis use (Sami et al., 2018).

Ongoing cannabis use influences disease course in individuals diagnosed with psychosis:

"What about use in people who have already been diagnosed with a psychotic disorder?" Ongoing cannabis use in people with psychotic disorders has been shown to be associated with more frequent relapses, more frequent hospitalizations, worse depressive symptoms and in some studies, greater positive symptoms in users compared to non-users with psychosis (Schoeler et al., 2016, Patel et al., 2016, Hadden et al., 2016, Toftdahl et al., 2016). Longer term follow-up in patients suggest that after the first year in an early intervention service (a time when symptoms will often stabilize), cannabis use may be associated with poorer outcomes than cocaine and methamphetamine abuse (Ouellet-Plamondon et al., 2017).

Gender differences:

"Did you know that there are sex differences in how we react to cannabis?" It is well known from drug use surveys that males tend to use more recreational drugs than females ((CTADS), 2015). Unfortunately, this may be masking some troubling trends that are being newly researched. In early phase psychosis, females usually have a later age of onset than males. However, while not well studied yet, female cannabis users may actually develop an earlier onset of psychosis (Allegri et al., 2013). There is also evidence that females who use cannabis may be less likely to quit and they report a lower quality of life than male cannabis users (Crocker and Tibbo, 2018). More research needs to be done on this topic. While there are gender differences that may exist with cannabis use and psychosis there is no current evidence for socioeconomic or ethnic differences.

Cannabis effects on co-occurring psychiatric conditions:

"What about those psychiatric conditions that can co-occur with psychosis?" People with psychosis can also have other psychiatric conditions. Overall, there is more research to be done

examining co-occurring disorders but our current understanding is that cannabis use can increase the risk for depression and some forms of anxiety disorder in people with psychosis (van der Meer and Velthorst, 2015). Ongoing cannabis use may also worsen symptoms of already diagnosed depression in individuals with psychosis (Hadden et al., 2016).

The adolescent use of cannabis may impact the development of anxiety and depression later in life. This field of research has very mixed results in part due to studies of weaker design such as those that include anyone who ever reported trying cannabis in their lifetime as a cannabis user and others that do not control for other substance use (Danielsson et al., 2016). Some groups have addressed these concerns by conducting meta-analyses that remove studies with weaker designs; and when this is done the body of research around depression, pooling data from 14 studies, demonstrated that cannabis use at early ages, particularly heavy use, was associated with an increased risk of depression (Lev-Ran et al., 2014). Cannabis use in adolescence may also increase the risk of suicide (Agrawal et al., 2017, Silins et al., 2014). A meta analysis examining the association between anxiety and cannabis use noted that the studies which adjusted for substance use, education and family situation found that adolescent cannabis use was associated with anxiety in young adulthood (Kedzior and Laeber, 2014). Further, recent well designed studies show that cannabis use is positively associated with symptoms of depression and, when begun in adolescence, can increase the risk of developing depression (Agrawal et al., 2017, Gage et al., 2015, Kerlin et al., 2018). It should be noted, however, that the strengths of these associations are not as strong as the association of daily or near daily adolescent cannabis use with psychosis development.

The addictive potential of cannabis:

"Can cannabis use cause addiction?" The answer is "Yes" (Blanco et al., 2016, Silins et al., 2014). On a scale of addiction potential, cannabis is assigned a low addictive potential value, often ranked with caffeine. An analogy can be made between the numbers of individuals requiring their morning cup of coffee and the potential number of individuals addicted to

cannabis. Cannabis use disorders may affect up to 30% of cannabis users (Hasin et al., 2015). We do know that younger age of starting cannabis use and use of high THC (also known as high potency) cannabis can increase the risk for developing a cannabis use disorder. Unfortunately, we do not currently have effective treatments for cannabis use disorders (Sabioni and Le Foll, 2018). This may become a greater concern as there is a movement towards managing opiod addictions with cannabis use (Hall et al., 2018, Reddon et al., 2018, Reiman et al., 2017, Vyas et al., 2018). This is an approach for which there is not yet sufficient data to support its efficacy (Hall et al., 2018, National Academies of Sciences and Medicine, 2017, Olfson et al., 2017, Zielinski et al., 2017, Franklyn et al., 2017)

Individuals who are dependent on cannabis will also experience withdrawal symptoms when they stop using such as anxiety, a strong sense of uneasiness, sleep disturbances, irritability, loss of appetite and in some cases, aggressive behavior(Sabioni and Le Foll, 2018, Smith et al., 2013).

Changes in cannabis potency over time:

Potency of cannabis was examined. While there are some methodological concerns around measurement techniques, it is estimated that in the 1970s cannabis contained <1.5% THC (ElSohly et al., 2000). By the 1980s, this amount had risen to 3.3% THC (ElSohly et al., 2000). By the 1990s, a small further increase to 4.3% THC had occurred (ElSohly et al., 2000). The amount of THC had jumped to 8% by the 2000s and 14.3% by the 2010s (ElSohly et al., 2016, Potter et al., 2018). Current estimates of THC potency are up to 28% and higher (Di Forti et al., 2015). This is important as it has been postulated that the earlier age of psychosis onset is attributable to this rise in THC content; an increase in the incidence of psychosis has been observed in regions where high potency cannabis is more prevalent and recent work has

demonstrated that increases in potency are a factor in increasing admissions for drug treatment (Freeman et al., 2018, Di Forti et al., 2015, Di Forti et al., 2014).

Motives for Cannabis use:

"Why do we smoke cannabis?" The reasons for taking cannabis vary from individual to individual and even use to use. Motivation to use can be broadly categorized. Enhancement motives can be thought of as adding excitement to your life and is often a motivation for initial recreational drug use. Social and conformity motives are two additional peer related categories that can influence use. Coping is a motive that is often applied to cannabis use in relation to self-soothing of negative states such as anxiety, depression, stress and even psychosis. Routine is an additional category of motive, a motive that can be avoided if individuals have activities and interests in their lives. There has been some recent research reported on motivations to use cannabis, including a systematic review (Schlossarek et al., 2016). This overview suggested that early onset of use (11-15 years of age), regular use that was not related to social motives, and use to cope with stressful life events were all risk factors for developing a cannabis use disorder. Conformity motives predicted use of cannabis but not dependence. Coping may be a motive more often used by women when deciding to use cannabis (Tu et al., 2008),while routine and conformity are often motives for men to use cannabis (Tu et al., 2008). Most concerning is recent evidence that use patterns in adolescence are not only leading to psychosis development but also potentially increasing the severity of the schizophrenia spectrum disorder (Shahzade et al., 2018). Additionally, there are studies that suggest having a mental illness might be a risk factor for developing a cannabis use disorder but these were mixed. This makes it unclear if people use cannabis to self-medicate in relation to their mental disorder.

References:

(CTADS), C. T. A. A. D. U. S. 2015. Canadian Tobacco Alcohol and Drugs (CTADS): 2015 summary [Online]. Government of Canada. Available: https://www.canada.ca/en/health-canada/services/canadian-tobacco-alcohol-drugs-survey/2015-summary.html [Accessed March 27, 2018 2018].

AGRAWAL, A., NELSON, E. C., BUCHOLZ, K. K., TILLMAN, R., GRUCZA, R. A., STATHAM, D. J., MADDEN, P. A., MARTIN, N. G., HEATH, A. C. & LYNSKEY, M. T. 2017. Major depressive disorder, suicidal thoughts and behaviours, and cannabis involvement in discordant twins: a retrospective cohort study. Lancet Psychiatry, 4, 706-714.

AGUILAR, D. D., GIUFFRIDA, A. & LODGE, D. J. 2018. Adolescent synthetic cannabinoid exposure produces enduring changes in dopamine neuron activity in a rodent model of schizophrenia susceptibility. Int J Neuropsychopharmacol.

ALLEGRI, F., BELVEDERI MURRI, M., PAPARELLI, A., MARCACCI, T., BRACA, M., MENCHETTI, M., MICHETTI, R., BERARDI, D. & TARRICONE, I. 2013. Current cannabis use and age of psychosis onset: a gender-mediated relationship? Results from an 8-year FEP incidence study in Bologna. Psychiatry Res, 210, 368-70.

ANDREASSON, S., ALLEBECK, P., ENGSTROM, A. & RYDBERG, U. 1987. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet, 2, 1483-6.

BHATIA, T., GETTIG, E. A., GOTTESMAN, I. I., BERLINER, J., MISHRA, N. N., NIMGAONKAR, V. L. & DESHPANDE, S. N. 2016. Stratifying empiric risk of schizophrenia among first degree relatives using multiple predictors in two independent Indian samples. Asian journal of psychiatry, 24, 79-84.

BLANCO, C., HASIN, D. S., WALL, M. M. & ET AL. 2016. Cannabis use and risk of psychiatric disorders: Prospective evidence from a us national longitudinal study. JAMA Psychiatry, 73, 388-395.

CROCKER, C. E. & TIBBO, P. G. 2015. Cannabis and the maturing brain: Role in psychosis development. Clin Pharmacol Ther, 97, 545-7.

CROCKER, C. E. & TIBBO, P. G. 2018. The interaction of gender and cannabis in early phase psychosis. Schizophr Res, 194, 18-25.

DANIELSSON, A.-K., LUNDIN, A., AGARDH, E., ALLEBECK, P. & FORSELL, Y. 2016. Cannabis use, depression and anxiety: A 3-year prospective population-based study. Journal of Affective Disorders, 193, 103-108.

DI FORTI, M., MARCONI, A., CARRA, E., FRAIETTA, S., TROTTA, A., BONOMO, M., BIANCONI, F., GARDNER-SOOD, P., O'CONNOR, J., RUSSO, M., STILO, S. A., MARQUES, T. R., MONDELLI, V., DAZZAN, P., PARIANTE, C., DAVID, A. S., GAUGHRAN, F., ATAKAN, Z., IYEGBE, C., POWELL, J., MORGAN, C., LYNSKEY, M. & MURRAY, R. M. 2015. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry, 2, 233-8.

DI FORTI, M., SALLIS, H., ALLEGRI, F., TROTTA, A., FERRARO, L., STILO, S. A., MARCONI, A., LA CASCIA, C., REIS MARQUES, T., PARIANTE, C., DAZZAN, P., MONDELLI, V., PAPARELLI, A., KOLLIAKOU, A., PRATA, D., GAUGHRAN, F., DAVID, A. S., MORGAN, C., STAHL, D., KHONDOKER, M., MACCABE, J. H. & MURRAY, R. M. 2014. Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users. Schizophr Bull.

DIAZ-ALONSO, J., GUZMAN, M. & GALVE-ROPERH, I. 2012. Endocannabinoids via CB(1) receptors act as neurogenic niche cues during cortical development. Philos Trans R Soc Lond B Biol Sci, 367, 3229-41.

ELSOHLY, M. A., MEHMEDIC, Z., FOSTER, S., GON, C., CHANDRA, S. & CHURCH, J. C. 2016. Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States. Biol Psychiatry, 79, 613-9.

ELSOHLY, M. A., ROSS, S. A., MEHMEDIC, Z., ARAFAT, R., YI, B. & BANAHAN, B. F., 3RD 2000. Potency trends of delta9-THC and other cannabinoids in confiscated marijuana from 1980-1997. J Forensic Sci, 45, 24-30.

FISCHER, B., RUSSELL, C., SABIONI, P., VAN DEN BRINK, W., LE FOLL, B., HALL, W., REHM, J. & ROOM, R. 2017. Lower-Risk Cannabis Use Guidelines: A Comprehensive Update of Evidence and Recommendations. Am J Public Health, 107, 1277.

FRANKLYN, A. M., EIBL, J. K., GAUTHIER, G. J. & MARSH, D. C. 2017. The impact of cannabis use on patients enrolled in opioid agonist therapy in Ontario, Canada. PLoS One, 12, e0187633.

FREEMAN, T. P., VAN DER POL, P., KUIJPERS, W., WISSELINK, J., DAS, R. K., RIGTER, S., VAN LAAR, M., GRIFFITHS, P., SWIFT, W., NIESINK, R. & LYNSKEY, M. T. 2018. Changes in cannabis potency and first-time admissions to drug treatment: a 16-year study in the Netherlands. Psychol Med, 1-7.

GAGE, S. H., HICKMAN, M., HERON, J., MUNAFÒ, M. R., LEWIS, G., MACLEOD, J. & ZAMMIT, S. 2015. Associations of cannabis and cigarette use with depression and anxiety at age 18: findings from the Avon Longitudinal Study of Parents and Children. PloS one, 10, e0122896.

GILMAN, J. M., KUSTER, J. K., LEE, S., LEE, M. J., KIM, B. W., MAKRIS, N., VAN DER KOUWE, A., BLOOD, A. J. & BREITER, H. C. 2014. Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. J Neurosci, 34, 5529-38.

HADDEN, K. L., LEDREW, K., HOGAN, K. & THOMAS, B. 2016. Impact of comorbid cannabis use on outcome in first episode psychosis. Early Interv Psychiatry.

HALL, W., WEST, R., MARSDEN, J., HUMPHREYS, K., NEALE, J. & PETRY, N. 2018. It is premature to expand access to medicinal cannabis in hopes of solving the US opioid crisis. Addiction, 0.

HASIN, D. S., SAHA, T. D., KERRIDGE, B. T., GOLDSTEIN, R. B., CHOU, S. P., ZHANG, H., JUNG, J., PICKERING, R. P., RUAN, W. J., SMITH, S. M., HUANG, B. & GRANT, B. F. 2015. Prevalence of Marijuana Use Disorders in the United States Between 2001–2002 and 2012–2013. JAMA psychiatry, 72, 1235-1242.

HELLE, S., RINGEN, P. A., MELLE, I., LARSEN, T. K., GJESTAD, R., JOHNSEN, E., LAGERBERG, T. V., ANDREASSEN, O. A., KROKEN, R. A., JOA, I., TEN VELDEN HEGELSTAD, W. & LOBERG, E. M. 2016. Cannabis use is associated with 3years earlier onset of schizophrenia spectrum disorder in a naturalistic, multi-site sample (N=1119). Schizophr Res, 170, 217-21.

HENQUET, C., KRABBENDAM, L., SPAUWEN, J., KAPLAN, C., LIEB, R., WITTCHEN, H.-U. & VAN OS, J. 2005. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ : British Medical Journal, 330, 11-11.

HERTING, M. M., GAUTAM, P., SPIELBERG, J. M., KAN, E., DAHL, R. E. & SOWELL, E. R. 2014. The role of testosterone and estradiol in brain volume changes across adolescence: a longitudinal structural MRI study. Hum Brain Mapp, 35, 5633-45.

JACOBUS, J. & TAPERT, S. F. 2014. Effects of Cannabis on the Adolescent Brain. Current pharmaceutical design, 20, 2186-2193.

KEDZIOR, K. K. & LAEBER, L. T. 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population--a meta-analysis of 31 studies. BMC Psychiatry, 14, 136.

KERLIN, A. M., LONG, M., KAPPELMAN, M., MARTIN, C. & SANDLER, R. S. 2018. Profiles of Patients Who Use Marijuana for Inflammatory Bowel Disease. Dig Dis Sci.

LARGE, M., SHARMA, S., COMPTON, M. T., SLADE, T. & NIELSSEN, O. 2011. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch Gen Psychiatry, 68, 555-61.

LEV-RAN, S., ROERECKE, M., LE FOLL, B., GEORGE, T. P., MCKENZIE, K. & REHM, J. 2014. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psychol Med, 44, 797-810.

LØBERG, E.-M., HELLE, S., NYGÅRD, M., BERLE, J. Ø., KROKEN, R. A. & JOHNSEN, E. 2014. The Cannabis Pathway to Non-Affective Psychosis may Reflect Less Neurobiological Vulnerability. Frontiers in Psychiatry, 5.

LU, H. C. & MACKIE, K. 2016. An Introduction to the Endogenous Cannabinoid System. Biol Psychiatry, 79, 516-25.

MALONE, D. T., HILL, M. N. & RUBINO, T. 2010. Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models. Br J Pharmacol, 160, 511-22.

MARCONI, A., DI FORTI, M., LEWIS, C. M., MURRAY, R. M. & VASSOS, E. 2016. Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. Schizophr Bull, 42, 1262-9.

MUSTONEN, A., NIEMELA, S., NORDSTROM, T., MURRAY, G. K., MAKI, P., JAASKELAINEN, E. & MIETTUNEN, J. 2018. Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis. Br J Psychiatry, 212, 227-233.

MYLES, H., MYLES, N. & LARGE, M. 2016. Cannabis use in first episode psychosis: Meta-analysis of prevalence, and the time course of initiation and continued use. Aust N Z J Psychiatry, 50, 208-19.

NATIONAL ACADEMIES OF SCIENCES, E. & MEDICINE 2017. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research, Washington, DC, The National Academies Press.

OLFSON, M., WALL, M. M., LIU, S.-M. & BLANCO, C. 2017. Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States. American Journal of Psychiatry, 175, 47-53.

ORR, J. M., PASCHALL, C. J. & BANICH, M. T. 2016. Recreational marijuana use impacts white matter integrity and subcortical (but not cortical) morphometry. Neuroimage Clin, 12, 47-56.

OUELLET-PLAMONDON, C., ABDEL-BAKI, A., SALVAT, E. & POTVIN, S. 2017. Specific impact of stimulant, alcohol and cannabis use disorders on first-episode psychosis: 2-year functional and symptomatic outcomes. Psychol Med, 47, 2461-2471.

PATEL, R., WILSON, R., JACKSON, R., BALL, M., SHETTY, H., BROADBENT, M., STEWART, R., MCGUIRE, P. & BHATTACHARYYA, S. 2016. Association of cannabis use with hospital admission and antipsychotic threatment failure in first episode psychosis: an observational study. BMJ Open, 6, 6:e009888.

PAUSELLI, L., BIRNBAUM, M. L., VAZQUEZ JAIME, B. P., PAOLINI, E., KELLEY, M. E., BROUSSARD, B. & COMPTON, M. T. 2018. Demographic and socioenvironmental predictors of premorbid marijuana use among patients with first-episode psychosis. Schizophr Res.

POTTER, D. J., HAMMOND, K., TUFFNELL, S., WALKER, C. & DI FORTI, M. 2018. Potency of Delta(9) -tetrahydrocannabinol and other cannabinoids in cannabis in England in 2016: Implications for public health and pharmacology. Drug Test Anal.

PROAL, A. C., FLEMING, J., GALVEZ-BUCCOLLINI, J. A. & DELISI, L. E. 2014. A Controlled Family Study of Cannabis Users with and without Psychosis. Schizophrenia research, 152, 283-288.

REDDON, H., DEBECK, K., SOCIAS, M. E., DONG, H., WOOD, E., MONTANER, J., KERR, T. & MILLOY, M. J. 2018. Cannabis use is associated with lower rates of initiation of injection drug use among street-involved youth: A longitudinal analysis. Drug and Alcohol Review, 37, 421-428.

REIMAN, A., WELTY, M. & SOLOMON, P. 2017. Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report. Cannabis Cannabinoid Res, 2, 160-166.

RODRIGUES, R. S., RIBEIRO, F. F., FERREIRA, F., VAZ, S. H., SEBASTIAO, A. M. & XAPELLI, S. 2017. Interaction between Cannabinoid Type 1 and Type 2 Receptors in the Modulation of Subventricular Zone and Dentate Gyrus Neurogenesis. Front Pharmacol, 8, 516.

SABIONI, P. & LE FOLL, B. 2018. Psychosocial and pharmacological interventions for the treatment of cannabis use disorder. F1000Research, 7, 173.

SAMI, M., NOTLEY, C., KOUIMTSIDIS, C., LYNSKEY, M. & BHATTACHARYYA, S. 2018. Psychotic-like experiences with cannabis use predict cannabis cessation and desire to quit: a cannabis discontinuation hypothesis. Psychol Med, 1-10.

SCHLOSSAREK, S., KEMPKENSTEFFEN, J., REIMER, J. & VERTHEIN, U. 2016. Psychosocial Determinants of Cannabis Dependence: A Systematic Review of the Literature. European Addiction Research, 22, 131-144.

SCHOELER, T., PETROS, N., DI FORTI, M., KLAMERUS, E., FOGLIA, E., AJNAKINA, O., GAYER-ANDERSON, C., COLIZZI, M., QUATTRONE, D., BEHLKE, I., SHETTY, S., MCGUIRE, P., DAVID, A. S., MURRAY, R. & BHATTACHARYYA, S. 2016. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. Lancet Psychiatry, 3, 947-953.

SHAH, D., CHAND, P., BANDAWAR, M., BENEGAL, V. & MURTHY, P. 2017. Cannabis induced psychosis and subsequent psychiatric disorders. Asian J Psychiatr, 30, 180-184.

SHAHZADE, C., CHUN, J., DELISI, L. E. & MANSCHRECK, T. C. 2018. Patterns in adolescent cannabis use predict the onset and symptom structure of schizophrenia-spectrum disorder. Schizophr Res.

SILINS, E., HORWOOD, L. J., PATTON, G. C., FERGUSSON, D. M., OLSSON, C. A., HUTCHINSON, D. M., SPRY, E., TOUMBOUROU, J. W., DEGENHARDT, L., SWIFT, W., COFFEY, C., TAIT, R. J., LETCHER, P., COPELAND, J. & MATTICK, R. P. 2014. Young adult sequelae of adolescent cannabis use: an integrative analysis. The Lancet Psychiatry, 1, 286-293.

SMITH, P. H., HOMISH, G. G., LEONARD, K. E. & COLLINS, R. L. 2013. Marijuana withdrawal and aggression among a representative sample of U.S. marijuana users. Drug and alcohol dependence, 132, 63-68.

STARZER, M. S. K., NORDENTOFT, M. & HJORTHOJ, C. 2017. Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis. Am J Psychiatry, appiajp201717020223.

TOFTDAHL, N. G., NORDENTOFT, M. & HJORTHOJ, C. 2016. The Effect of Changes in Cannabis Exposure on Psychotic Symptoms in Patients With Comorbid Cannabis Use Disorder. J Dual Diagn, 12, 129-36.

TU, A. W., RATNER, P. A. & JOHNSON, J. L. 2008. Gender Differences in the Correlates of Adolescents' Cannabis Use. Substance Use & Misuse, 43, 1438-1463.

VAN DER MEER, F. J. & VELTHORST, E. 2015. Course of cannabis use and clinical outcome in patients with non-affective psychosis: a 3-year follow-up study. Psychol Med, 45, 1977-88.

VAN OS, J., BAK, M., HANSSEN, M., BIJL, R. V., DE GRAAF, R. & VERDOUX, H. 2002. Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol, 156, 319-27.

VYAS, M. B., LEBARON, V. T. & GILSON, A. M. 2018. The use of cannabis in response to the opioid crisis: A review of the literature. Nurs Outlook, 66, 56-65.

ZIELINSKI, L., BHATT, M., SANGER, N., PLATER, C., WORSTER, A., VARENBUT, M., DAITER, J., PARE, G., MARSH, D. C. & DESAI, D. 2017. Association between cannabis use and methadone

maintenance treatment outcomes: an investigation into sex differences. Biology of sex differences, 8, 8.