

# Clearing the Smoke on Cannabis

## Regular Use and Mental Health

**Sarah Konefal, Ph.D.**, Research and Policy Analyst, CCSA

**Robert Gabrys, Ph.D.**, Research and Policy Analyst, CCSA

**Amy Porath, Ph.D.**, Director, Research, CCSA

### Key Points

- Regular cannabis use refers to weekly or more frequent cannabis use over a period of months to years.
- Regular cannabis use is at least twice as common among individuals with mental disorders, including schizophrenia, bipolar disorders, depressive and anxiety disorders, and post-traumatic stress disorder (PTSD).
- There is strong evidence linking chronic cannabis use to increased risk of developing psychosis and schizophrenia among individuals with a family history of these conditions.
- Although smaller, there is still a risk of developing psychosis and schizophrenia with regular cannabis use among individuals without a family history of these disorders. Other factors contributing to increased risk of developing psychosis and schizophrenia are early initiation of use, heavy or daily use and the use of products high in THC content.
- The risk of developing a first depressive episode among individuals who use cannabis regularly is small after accounting for the use of other substances and common sociodemographic factors. However, cannabis use can increase the risk of suicidality even in the absence of a pre-existing condition.
- The risk of developing an anxiety disorder following regular cannabis use is also low. However, individuals with certain anxiety disorders (e.g., social anxiety) tend to self-medicate using cannabis and are at an increased risk of developing a cannabis use disorder.
- Cannabis use is associated with poorer mental health outcomes in PTSD and individuals with PTSD often present with problematic cannabis use and cannabis use disorders. However, there is a lack of studies controlling for previous cannabis use and baseline symptom severity in individuals with PTSD.
- To understand better the effects of regular cannabis use on mental health, researchers need a standardized measurement of cannabis use, in addition to larger, well-designed prospective studies. Research must also keep in mind polysubstance use, genetic background, and sex and gender differences.

*This is the first in a series of reports that reviews the effects of cannabis use on various aspects of human functioning and development. This report on the effects of regular cannabis use on mental health provides an update of a previous report with new research findings that validate and extend our current understanding of this issue. Other reports in this series address the link between regular cannabis use and cognitive functioning, the effects of maternal cannabis use during pregnancy, cannabis use and driving, the respiratory effects of cannabis use and the medical use of cannabis and cannabinoids. This series is intended for a broad audience, including health professionals, policy makers and researchers.*



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### **Regular and Heavy Cannabis Use**

*Although there is no single definition in the scientific literature as to what constitutes regular cannabis use, the phrase generally refers to a pattern that entails weekly or more frequent use over periods of months or years and poses a risk for adverse health effects. Terms that are often used interchangeably with regular use include frequent use, chronic use and long-term use. Heavy use, by contrast, typically refers to daily or more frequent use, and can be a sign of dependence and cannabis use disorder.*

## **Background**

Cannabis is one of the most widely used psychoactive substances in Canada. According to the 2017 Canadian Tobacco, Alcohol and Drugs Survey (CTADS), 14.8% of Canadians aged 15 years and older reported using cannabis at least once in the past year (Health Canada, 2018). The use of cannabis is generally more prevalent among young people, with 20.6% of youth aged 15 to 19 and 29.7% of young adults aged 20 to 24 reporting past-year use. Approximately 72% of Canadians aged 15 and older who used cannabis in the past year reported using it in the past three months, and 33% reported using cannabis on a daily or almost daily basis.

The complex relationship between cannabis use and mental disorders has garnered significant attention as a public health issue. National survey data indicate that substance use disorders (SUDs) have a high comorbidity with mental illness (Khan, 2017) and that problematic cannabis use is more prevalent among individuals with mental health disorders (Hango & LaRochelle-Côté, 2018; Statistics Canada, 2013). For many mental health disorders, there is not enough evidence to determine the extent to which regular cannabis use contributes directly to developing the disorder. The link between regular cannabis use and mental health disorders is complex, as associations can be accounted for by overlapping environmental (e.g., low socioeconomic status, adverse childhood experiences) and genetic (e.g., family history of psychiatric disorders) risk factors that underlie both problematic cannabis use and mental illness. In addition, problematic cannabis use and mental health disorders share similar neurobiological features, including dysregulation of neurotransmitters (e.g., dopamine) and alterations in brain structure and

*Cannabis refers to products of the cannabis plant *Cannabis sativa*. It is usually a greenish or brownish material consisting of the dried flowering fruiting tops and leaves of the cannabis plant. Hashish or cannabis resin is the dried brown or black resinous secretion of the flowering tops of the cannabis plant. Shatter and wax are two types of highly potent cannabis extracts, typically called concentrates, that are made in labs using various chemical solvents. Cannabis can be consumed by smoking, vaporization, ingestion (edibles), oral application of tinctures, and topical application of creams, oils and lotions.*

*Cannabis consists of more than 100 cannabinoids, with delta-9-tetrahydrocannabinol (THC) being the main psychoactive ingredient responsible for the “high” feeling. Cannabidiol (CBD) is another important cannabinoid that indirectly modulates the brain’s endocannabinoid system and might have more beneficial effects. The acute effects of cannabis include euphoria and relaxation, changes in perception, time distortion, deficits in attention span and memory, increased heart rate and blood pressure, and impaired motor functioning. Consuming a large dose of THC or a highly concentrated cannabis product can induce acute psychosis, which includes delusions, paranoia and dissociation. This effect can occur even in individuals with no history of mental illness.*

*Over the past few decades, there has been an increase in the concentrations of THC (and decrease in CBD levels) in illicit cannabis, increasing from 4% in 1995 to 12% in 2014 (El Sohly et al., 2016). Canada legalized the use of cannabis for non-medical purposes for adults on October 17, 2018.<sup>1</sup> A review of Canadian online cannabis retail outlets (e.g., ocs.ca, bccannabisstores.com, albertacannabis.org, etc.) revealed that dried cannabis products have up to 30% THC and products in the 15% to 20% THC range are common.*

function. Problematic cannabis use and mental illnesses could co-occur with no causal relationship because they have overlapping neurobiological underpinnings, including genetic predisposition. More research is needed in this area.

<sup>1</sup> Each province and territory is responsible for developing its own regulations for the sales and distribution of cannabis, and can add additional restrictions to the federal legislation, such as increasing the age of access. Age of access is 19 in most provinces and territories, except for Alberta and Quebec where the legal age of access is 18.

While regular cannabis use can develop into a cannabis use disorder (CUD), an individual can engage in regular cannabis use without having a CUD. Likewise, an individual who uses cannabis less frequently might present with a severe CUD (see Diagnostic Criteria for Cannabis Use Disorder textbox). From this perspective, it is currently unclear how much of the relationship between CUD and mental illness is accounted for by cannabis use (i.e., the effects of cannabinoids on the brain) and how much is attributable to other factors, including the presence of health and social stressors that accompany a CUD.

This report — part of a series reviewing the effects of cannabis use on various aspects of human health and development (see Beirness & Porath-Waller, 2017; Gabrys & Porath, 2019; Kalant & Porath-Waller, 2016; Konefal, Kent & Porath, 2018; McInnis & Plecas, 2016) — provides an update on impacts of regular cannabis use on various aspects of mental health. This report also compliments and extends the position statement of the Canadian Psychiatric Association (CPA) around the effects of cannabis use on mental health (Tibbo et al., 2018). Following a review of the evidence, this report discusses implications for policy and practice.

## Schizophrenia and Psychosis

Schizophrenia is characterized by abnormalities in thinking, perception, emotions, sense of self and behaviour. It is hypothesised to be a neurodevelopmental disorder and includes alterations in brain circuit structure and function, with symptoms manifesting in early adulthood. A key symptom of schizophrenia is psychosis, an acute event characterized by cognitive disengagement from reality that often involves delusions or hallucinations. A first episode of psychosis can be the first sign of schizophrenia, especially in subjects with a family history of mental disorders. However, an individual can have psychosis without having been diagnosed with schizophrenia and psychosis can be a symptom of other psychiatric diagnoses such as bipolar disorder. Studies evaluating the link between cannabis use and psychotic disorders are not always diagnosis-specific. In several studies, the diagnosis of schizophrenia or first episode of psychosis is used. Using the first episode of psychosis as a diagnostic outcome groups schizophrenia, bipolar disorder and other psychotic disorders together.

The prevalence of cannabis use and CUD is significantly higher among individuals with schizophrenia compared to the general population (Hunt, Large, Cleary, Lai, & Saunders, 2018; McLoughlin et al., 2014). There is substantial evidence to suggest that regular cannabis use leads to increased occurrence of schizophrenia and psychosis (Gage et al., 2017; Marconi, Di Forti, Lewis, Murray, & Vassos, 2016; Moore et al., 2007; Myles, Newall, Nielssen, & Large, 2012;

National Academies of Sciences, Engineering, and Medicine, 2017). This association is still present even after adjusting for a variety of confounding factors such as other substance use, sociodemographics, personality and other mental health conditions. It has been estimated that using cannabis at some point in life increases the risk for developing psychosis by 40% (Henquet, Murray, Linszen, & van Os, 2005) and that cannabis use accounts for 8–14% of diagnoses of schizophrenia (Moore et al., 2007).

Among commonly used substances, cannabis may be one of the more risky to use in terms of increasing an individual's risk for schizophrenia. A longitudinal study in Denmark demonstrated that, after adjusting for other types of SUDs, a diagnosis of CUD had the largest association with schizophrenia diagnoses for up to 10–15 years, followed by alcohol (Nielsen, Toftdahl, Nordentoft, & Hjorthøj, 2017). Similarly, among patients accessing addiction services, there was a significantly higher risk of schizophrenia among individuals with CUD compared to those with cocaine use disorder (Libuy, de Angel, Ibáñez, Murray, & Mundt, 2018).

The degree of risk contributed by chronic cannabis use is influenced by family history of mental illness, how frequent someone uses cannabis, age at which they began using cannabis, the concentration of THC in the cannabis and the ratio of THC to CBD in the cannabis. The relationship between frequency of cannabis use and the first episode of psychosis is dose-dependent in that more frequent cannabis use is predictive of an increased risk for psychotic outcomes (Andréasson, Engström, Allebeck, & Rydberg, 1987; Di Forti et al., 2015; Di Forti et al., 2009; Di Forti et al., 2014; Karcher et al., 2019; Marconi et al., 2016; Moore et al., 2007; Zammit, Allebeck, Andréasson, Lundberg, & Lewis, 2002). Individuals who initiate cannabis use early, particularly in adolescence, also increase their risk for developing psychotic disorders (Arseneault et al., 2002; Hanna, Perez, & Ghose, 2017; Hosseini & Oremus, 2018; Levine, Clemenza, Rynn, & Lieberman, 2017). Initiating cannabis use in adolescence is also associated with an earlier age of schizophrenia (Casadio, Fernandes, Murray, & Di Forti, 2011; Malone, Hill, & Rubino, 2010) and psychosis (Kuepper, Van Os, Lieb, Wittchen, & Henquet, 2011;). Using cannabis with higher THC content and lower CBD content also adds to this risk (Di Forti et al., 2009; Di Forti et al., 2014). As evidence for this increased risk, a recent case-control study was able to assess for the first time whether differences in regular cannabis use relate to the incidence (frequency) of psychotic disorders (Di Forti et al., 2019). The authors found that the incidence of psychotic disorders was higher in geographic locations where individuals used cannabis daily and used cannabis high in THC, as compared with locations where individuals used less potent cannabis and used it less frequently.

Having an immediate family member with schizophrenia is one of the strongest known risk factors for developing schizophrenia and related psychotic disorders (Misiak et al., 2018; Schizophrenia Working Group of the Psychiatric Genomics et al., 2014; DeVylder & Lukens, 2013). However, the majority of individuals who develop schizophrenia do not have a family history of schizophrenia. Chronic cannabis use is more likely to result in schizophrenia in individuals with a family history of the illness compared to individuals with no family history (Giordano, Ohlsson, Sundquist, Sundquist, & Kendler, 2015; Henquet et al., 2005; Proal, Fleming, Galvez-Buccollini, & DeLisi, 2014; van Os et al., 2002).

Genes regulating neurotransmission in the brain, particularly in dopaminergic pathways, modulate the interaction between cannabis use and psychotic disorders (Mané et al., 2017; Morgan, Freeman, Powell, & Curran, 2016; Verweij et al., 2017). Molecular genetic research demonstrates that gene variants influence the likelihood of psychotic disorders in individuals who have used cannabis, including an earlier onset of psychotic symptoms (Caspi et al., 2005; Colizzi et al., 2015; Estrada et al., 2011; Lodhi et al., 2017; Pelayo-Terán et al., 2010). Although genetic risk factors underlie both the likelihood of developing schizophrenia and initiating cannabis use (Power et al., 2014; Verweij et al., 2017), frequent and problematic cannabis use is still an independent risk factor for developing psychotic disorders. Among twin and non-twin sibling pairs, psychotic-like experiences were more common in individuals who had either frequently used cannabis or who had ever been diagnosed with a CUD (Karcher et al., 2019). This study also found that, to a lesser degree, psychotic-like experiences were also associated with current cannabis use (Karcher et al., 2019).

There has generally been less investigation into the neurobiological effects of cannabis in individuals already diagnosed with a psychotic disorder. Psychosis patients who use cannabis can have distinct clinical and neurocognitive features compared with patients who do not use cannabis. These distinct features are particularly apparent among individuals with a lifetime history of cannabis use or who initiated cannabis use earlier (e.g., before age 17) (Myles et al., 2012; Yücel et al., 2010). For example, early initiation of cannabis use is associated with compromised structural connectivity between brain regions and these abnormalities parallel changes in connectivity associated with the onset of schizophrenia (Cookey, Bernier, & Tibbo, 2014). Most studies evaluating the effects of cannabis use among patients with psychotic disorders have not appropriately controlled for a range of confounding factors such as previous cannabis use or severity of symptoms.

Of further interest for this review is that CBD administration has been hypothesized to have antipsychotic properties, properties that counteract the effects of THC and improve symptoms of psychosis that might be associated with THC (Englund, Freeman, Murray, & McGuire, 2017; Guimaraes, Rodrigues, Silva, & Gomes, 2018; Iseger & Bossong, 2015). However, there have been no large-scale clinical trials to examine whether CBD is an effective treatment for symptoms of psychosis or schizophrenia. Two small placebo-controlled trials of CBD conducted in patients with schizophrenia reveal mixed results. One study reported no significant effect of CBD treatment for six weeks on cognitive or psychotic outcomes (Boggs et al., 2018), while another reported that CBD treatment for six weeks improved psychotic symptoms, cognitive performance and overall wellbeing (McGuire et al., 2017).

Differences in sex and gender are relevant to the interaction between regular cannabis use and the development or symptomology of schizophrenia and psychosis. First, cannabis use, especially frequent use, is more prevalent among males across all ages (Health Canada, 2018). Cannabis use is also more prevalent among males with first episode psychosis or schizophrenia (Lange et al., 2014; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). Second, sex differences play an important role in the presentation of clinical symptomology of psychosis and schizophrenia (Barajas, Ochoa, Obiols, & Lalucat-Jo, 2015; Filatova et al., 2017). For example, it is well established that the age of onset for psychosis or schizophrenia is earlier in males compared to females (Dekker et al., 2012; ElTayebani, ElGamal, Roshdy, & Al-Khadary, 2014; Ochoa et al., 2012). Third, these sex and gender differences in symptoms might be influenced by comorbid SUDs (Segarra et al., 2012), and cannabis use specifically might differentially affect males and females in relation to psychosis and schizophrenia (Crocker & Tibbo, 2018). There is emerging research to suggest that the age difference for psychosis onset observed in males and females could be explained by higher rates of cannabis use among males (Allegri et al., 2013; Crocker & Tibbo, 2018; Rabinowitz et al., 1998).

Collectively, the available evidence suggests a strong relationship between cannabis use and increased risk of psychosis and schizophrenia, especially among individuals who initiated cannabis use early in life or have a family history of psychotic disorders. It should be emphasized that regular cannabis use also increases the risk of psychotic symptoms among individuals without a family history of psychotic disorders, especially among individuals who use cannabis heavily and use cannabis products high in THC.

### **Diagnostic Criteria for Cannabis Use Disorder**

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (American Psychiatric Association, 2013, cited as DSM-5) defines “cannabis use disorder” as “a problematic pattern of use leading to clinically significant impairment or distress.” The DSM-5 diagnostic criteria for the disorder include:

- Using more cannabis than intended and trying unsuccessfully to control use;
- Spending a significant amount of time obtaining and using cannabis or recovering from its effects;
- Experiencing a strong desire or urge to use cannabis;
- Failing to fulfill major obligations at work, home or school because of cannabis use;
- Giving up or reducing important social, occupational or recreational activities because of cannabis use;
- Continuing use despite recurring social, physical or psychological problems caused by cannabis;
- Using cannabis in physically hazardous situations;
- Increasing tolerance to cannabis' effects; and
- Developing withdrawal symptoms characterized by irritability, sleep disorders, anxiety, aggression, decrease appetite, weight loss and restlessness. Other symptoms include sweating, stomach pain, chill, shakiness and depression (DSM-5). Withdrawal symptoms can appear one to two weeks after discontinuing cannabis use, as THC has a long half-life (Huestis, 2005).

While regular cannabis use might be associated with a CUD or increase an individual's risk of developing a CUD, regular cannabis use and a CUD are not one in the same. The percentage of people who develop a CUD is not well established. In a study of first-year college students in the United States, about 24% of people who had used cannabis developed a CUD and another 33% met the criteria for a CUD but were undiagnosed (Caldeira, Arria, O'Grady, Vincent, & Wish, 2008). That frequency of cannabis use can be independent of a CUD is important for interpreting the findings presented in this report.

### **Depressive Disorders**

Depression, part of a collection of depressive disorders, is characterized by persistent depressed mood or anhedonia (i.e., lack of interest or pleasure in all or most activities). In addition to these symptoms, individuals with a depressive disorder can have difficulties in concentration and decisiveness, reduced energy, slowed thought and physical movement, changes in weight and sleep, feelings of worthlessness and guilt, and thoughts of death and recurrent suicidal ideation (DSM-5). Depression is a complex heterogeneous disorder, meaning that the combination, severity and persistence of depressive symptoms can vary among individuals, as can the factors that contribute to the onset of a depressive episode.

There is strong evidence indicating that depression is associated with CUD during early adolescence through to late adulthood, with the strength of the relationship slightly varying across an individual's life (Leadbeater, Ames, & Linden-Carmichael, 2019). The relationship is bidirectional, meaning that individuals with a CUD are at an increased risk of a depressive episode (Smolkina et al., 2017) and individuals who initiate cannabis use while experiencing

depressive symptoms are more likely to develop a CUD (Rhew et al., 2017). Although depression has been related to more frequent cannabis use among males (Assari, Mistry, Caldwell, & Zimmerman, 2018; Crane, Langenecker, & Mermelstein, 2015), the relationship between CUD and depression does not differ significantly between males and females (Foster, Li, McClure, Sonne, & Gray, 2016).

Several meta-analyses have examined whether cannabis use leads to developing depression, within several months or many years following the initiation of cannabis use. Results from these analyses indicate that cannabis use is associated with increased risk of developing depression. However, in the general population, the risk is relatively low, especially after accounting for confounding variables, including pre-morbid depression, alcohol and other substance use, age, sex, ethnicity and education (Gobbi et al., 2019; Lev-Ran et al., 2014; Mammen et al., 2018). These findings suggest that cannabis use and depression might be linked by common sociodemographic risk factors, and that in the general population most individuals who use cannabis regularly will not go on to develop a major depressive episode.

Although several studies controlling for premorbid depression do report an association between cannabis consumption and risk of depression, there is also substantial variability among studies (Gobbi et al., 2019). Furthermore, while most studies control for factors related to both regular cannabis use and depression, there has been relatively limited research examining how cannabis use might interact with known risk factors of depression, including socioeconomic status, early life adversity and genetic predisposition. Finally, it is still unknown whether and the degree to which repeated brain exposure to cannabinoids directly contributes to the emergence and persistence of depressive pathology (Lucatch, Coles, Hill, & George, 2018).

A number of studies have examined whether frequency of cannabis use (as opposed to the presence of a CUD) was associated with depression severity. Cannabis is a commonly used substance among individuals experiencing symptoms of depression (Leadbeater et al., 2019) and especially those seeking treatment for major depression (Bahorik et al., 2017). It is not well known how cannabis use affects the prognosis of depressive illness, but recent studies indicate that cannabis use worsened depression and contributed to poorer overall mental health among treatment seeking individuals (Bahorik et al., 2017; Mammen et al., 2018). Moreover, while 28 days of monitored abstinence from cannabis are associated with reductions in symptom severity (Jacobus et al., 2017), it is not clear whether discontinuing cannabis use alone is sufficient to result in remission of depression.

Several studies reported that depression was related to more frequent cannabis use among males (Assari et al., 2018; Crane et al., 2015), although an earlier study reported that frequent cannabis use among adolescent females predicted higher rates of depression (Patton et al., 2002). There is evidence that initiating cannabis before the age of 25 is associated with more severe symptoms of depression, especially among those with a pre-existing vulnerability to it (Hosseini & Oremus, 2018). Finally, treatment for CUD has been associated with improvements in depression (Hser et al., 2017), especially among individuals who present with more severe depressive symptoms (Moitra, Anderson, & Stein, 2016).

Although the link between cannabis use and the presence of depressive symptoms has frequently been reported, it has been more difficult to determine the extent to which depression leads to regular cannabis use or the extent to which regular cannabis use increases the risk of depressive

disorder. There is evidence suggesting that in some cases depression can lead to regular cannabis use (Bahorik et al., 2017; Wilkinson, Halpern, & Herring, 2016). The association between depression and frequent cannabis use might be partly related to the reasons why an individual uses cannabis. For example, relative to using cannabis recreationally or for social purposes, using cannabis to cope with negative emotions was associated with CUD, cannabis problem severity, depression and perceived stress (Moitra et al., 2016). In this respect, the presence of depression and frequent cannabis use (and a CUD) might be symptoms of stress and maladaptive coping efforts (e.g., Ketcherside & Filbey, 2015). More research is needed to determine why some depressed individuals engage in frequent cannabis use while others do not.

Individuals vary in the particular combination and severity of depressive symptoms they experience, as well as the factors that contribute to the onset of the illness. It appears that regular cannabis use is associated with certain depressive symptoms more than others, especially anhedonia and sleep disturbances (Bersani et al., 2016; Mammen et al., 2018). These findings are consistent with the role of cannabinoids in these behaviours (Babson, Sottile, & Morabito, 2017) and are in line with the disturbances in motivation and reward processes that have been observed among individuals who use cannabis chronically (see Gabrys & Porath, 2019). The findings suggest that regular cannabis use might be associated with a specific depressive profile, characterized by anhedonia and sleep disturbances. However, more studies are needed to characterize the depressive symptoms associated with cannabis use.

Taken together, the available evidence suggests that cannabis use and depression are related in a reciprocal fashion. However, from a population health perspective, the risk of developing depression among individuals who use cannabis is small, after accounting for common sociodemographic factors.

More research is needed to determine how individual-level risk factors, including genetic liability to depression and early life experiences, interact with cannabis use in promoting the evolution of depressive pathology. There is evidence that cannabis use is not beneficial to those diagnosed with depression. Given the strong link between depression and CUD, interventions aimed at alleviating symptoms of depression and education on adaptive strategies to cope with stressful experiences might prove useful for reducing cannabis use, as well as the harms associated with it.

## Bipolar Disorders

Bipolar disorders are characterized by periods of mania and hypomania followed by episodes of depression. Manic episodes include elevated, expansive and irritable mood in addition to inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, racing thoughts and flights of ideas, distractibility, and excessive pleasure seeking or risky activity (DSM-5). The intensity and length of manic and depressive episodes varies among individuals and types of bipolar disorder. The etiology of bipolar disorders is not well understood, although there appears to be a genetic link between psychotic disorders, including schizophrenia, and bipolar disorders (Craddock et al., 2005; Lake & Hurwitz, 2007).

Compared to other mental health conditions, there has been limited research examining the association between cannabis use and bipolar disorders. Similar to the pattern for other mental illnesses, individuals with bipolar disorder are more likely to use cannabis and develop CUD compared to the general population (Lev-Ran, Le Foll, McKenzie, George, & Rehm, 2013; Taub, Feingold, Rehm, & Lev-Ran, 2018). As well, cannabis use typically worsens clinical outcomes in those with bipolar disorder, including greater symptom severity and duration of manic phases (van Rossum, Boomsma, Tenback, Reed, & van Os, 2009; Strakowski, DelBello, Fleck, & Arndt, 2000; Baethge et al., 2008). A large longitudinal study in the United States indicated there was no association between any past-year cannabis use and the onset of bipolar disorder, after adjusting for use of alcohol and other substances (Feingold, Weiser, Rehm, & Lev-Ran, 2015). However, another study using data from the same cohort indicated that more regular cannabis use (e.g., weekly) was modestly associated with an increased risk for past-year bipolar disorder diagnosis (Cogle, Hakes, Macatee, Chavarria, & Zvolensky, 2015). A meta-analysis of just two studies showed an association between cannabis use and the onset of manic symptoms in individuals with no history of bipolar disorder (Gibbs et al., 2015). Cannabis use was also associated with an earlier age of onset of bipolar disorder (Bally, Zullino, & Aubry, 2014), exacerbated by childhood abuse (Aas et al., 2014).

Among individuals already diagnosed with bipolar disorder, there is some evidence to suggest that cannabis use worsens the course of the illness by increasing the time to recovery, and relapse and recurrence of manic episodes (Gibbs et al., 2015; Zorrilla et al., 2015). One longitudinal study of 4,815 individuals indicated that cannabis use was associated with greater expression of manic symptoms. This relationship remained after controlling for numerous variables, including age, sex, educational level, ethnicity,

single marital status, neuroticism, use of other drugs, use of alcohol, depressive symptoms and manic symptoms at baseline (Henquet, Krabbendam, de Graaf, ten Have, & van Os, 2006).

The available evidence indicates that cannabis use has a considerable negative impact on the course of bipolar disorder, and heavy cannabis use might trigger the first episode of bipolar disorder (Lagerberg et al., 2011). The association between cannabis use and first episode onset of bipolar disorder might be confounded by the resemblance of mania and hypomania symptoms to psychotic symptoms in younger individuals (Zorrilla et al., 2015).

## Anxiety Disorders

Anxiety disorders can take many forms, including generalized anxiety disorder, social anxiety and panic disorder (DSM-5). While some of the psychological and biological processes are common among anxiety disorders, each type has its own neurobiology underpinnings and is associated with specific risk factors. Generalized anxiety disorder is characterized by excessive and uncontrollable anxiety, as well as worry about a variety of topics, event or activities, that persists for long periods (e.g., six month or longer). This anxiety is often accompanied by cognitive and physical symptoms, including restlessness and irritability, impaired concentration, fatigue, muscle aches and soreness, and difficulty sleeping (DSM-5). Because most studies examining the relation between cannabis use and anxiety disorders have focused on generalized anxiety disorder — if specified at all — the term “anxiety” in this section refers to generalized anxiety disorder, unless otherwise specified.

Several studies have indicated an association between cannabis use and anxiety (Brook, Lee, Brown, Finch, & Brook, 2015; Degenhardt et al., 2013; Gage et al., 2015). An earlier large longitudinal study indicated that individuals who used cannabis were more likely to report symptoms of anxiety, especially when they initiated use before the age of 15 and continued to use through the age of 21 (Hayatbakhsh et al., 2007). A more recent study reported a similar link between cannabis use and anxiety that was apparent across most ages (i.e., 18 to 65 years of age) (Leadbeater et al., 2019). However, when controlling for confounding variables (e.g., other substance use, psychiatric illness, demographics), the relationship between anxiety and either cannabis use or a CUD is relatively small (Kedzior & Laeber, 2014; Twomey, 2017) or no longer present (Blanco et al., 2016; Feingold et al., 2015; Gage et al., 2015; Gobbi et al., 2019). These findings indicate that in the general population cannabis use has a minimal impact on the development of

anxiety disorder. Instead, it appears that similar risk factors (e.g., alcohol and other drug use, lower education, family tension, poor upbringing) link frequent cannabis use and anxiety disorder (Danielsson, Lundin, Agardh, Allebeck, & Forsell, 2016).

Although at a population level the impact of cannabis use on developing anxiety is small, the strength of this effect varies among individuals. For example, some individuals might engage in heavy cannabis use without developing an anxiety disorder. For other individuals, cannabis use can result in persistent anxiety, which then leads to increased use of cannabis as a self-medication strategy, and ultimately the development of CUD (Temple, Driver, & Brown, 2014). It is therefore important to identify which individuals are at most risk of developing an anxiety disorder once they have initiated cannabis use. There is some evidence indicating that females who frequently use cannabis are more likely to report anxiety than males (Patton et al., 2002), and an earlier age of cannabis use onset has been prospectively associated with developing anxiety (Duperrouzel et al., 2018). Furthermore, cannabis use was associated with an increase in symptoms of anxiety, but only in individuals carrying a gene variant related to increased risk of depression and anxiety (Otten, Huizink, Monshouwer, Creemers, & Onrust, 2017).

Similar to chronic cannabis use as a risk factor for developing anxiety, there is also a limited evidence base implicating anxiety disorders in the initiation of cannabis use (Kedzior & Laeber, 2014). The presence of an anxiety disorder, especially social anxiety disorder, appears to be an important risk factor for developing problematic cannabis use (Buckner & Zvolensky, 2014; Buckner et al., 2017). In fact, social anxiety disorder is related to cannabis dependence at rates more than twice that of other anxiety disorders, including generalized anxiety disorder, agoraphobia and panic disorder (Agosti, Nunes, & Levin, 2002). Some researchers have suggested that individuals with social anxiety disorder might be more likely to use cannabis to self-medicate their anxiety reactions than individuals with other anxiety disorders (Buckner & Zvolensky, 2014). Individuals with panic disorder, on the other hand, might avoid cannabis out of concern that using it will bring about a panic attack (Buckner et al., 2008).

There is little research to determine whether regular cannabis use actually affects symptoms of anxiety. One small prospective study among 18 to 21 year olds suggests that cannabis could indirectly modulate anxiety symptoms via association with temperament traits such as novelty seeking and harm avoidance (Grunberg, Cordova, Bidwell & Ito, 2015).

Collectively, these findings indicate that the frequency of cannabis use and motives for cannabis use (e.g., self-medication) vary across anxiety disorders. Further, addressing underlying anxiety symptoms among individuals who frequently use cannabis or present with a CUD might be an effective strategy for limiting the frequency of cannabis use (Buckner, Zvolensky, Ecker, & Jeffries, 2016).

*The brain produces its own natural compounds, called endocannabinoids, that act like THC. Endocannabinoids, which include anandamide (AEA) and 2-arachidonoylglycerol (2-AG), exert their effects by binding to cannabinoid (CB1 and CB2) receptors. Cannabinoid receptors are present throughout the brain and body, meaning that cannabinoids can influence a broad range of psychological and biological processes, such as cognition, emotional processing and regulation, stress response, appetite, immune functioning, the endocrine (hormone) system, sleep and pain signalling (Zou & Kumar, 2018). THC mimics the activity of AEA and binds at the CB1 receptors. It binds, however, at much higher levels than AEA itself, flooding the endocannabinoid system leading to altered functioning of each process. This flooding means that chronic use of cannabis (i.e., repeated brain exposure to THC) can alter the functioning of the endocannabinoid system, which can include changes in AEA and 2-AG activity, and the distribution of cannabinoid receptors (Jacobson, Watts, Boileau, Tong, & Mizrahi, 2019).*

## Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) results from exposure to a traumatic event or events and is characterized by persistent re-experiencing of the event, either through intrusive memories, flashbacks or nightmares, accompanied by intense emotional distress and physiological reactivity (e.g., elevated heart rate and blood pressure).

PTSD is highly comorbid with depressive and anxiety disorders, and is a significant risk factor for the development of SUDs, including CUD (Agosti et al., 2002; Bonn-Miller, Harris, & Trafton, 2012; Gentes et al., 2016; Gorelick, 2019). The prevalence of PTSD is higher among individuals with CUD compared to individuals with other SUDs (Bonn-Miller et al., 2012). Endocannabinoid signalling

is important for modulating fear-related memories and behaviours (Dincheva et al., 2015; Hariri et al., 2009; LeDoux, 2000; Rabinak et al., 2013; Rodrigues, Schafe, & LeDoux, 2004; Rogan, Stäubli, & LeDoux, 1997), and there is also a growing body of research demonstrating that PTSD results in long-lasting alterations to the brain's endocannabinoid system (Michopoulos, Norrholm, & Jovanovic, 2015; Neumeister et al., 2013; Pietrzak et al., 2014).

Genetic factors, “trauma load” (cumulative exposure to traumatic events) and co-morbidity of other psychiatric conditions are all established risk factors for PTSD (Almli, Fani, Smith, & Ressler, 2014; Pitman et al., 2012; Ross et al., 2017; Shishko, Oliveira, Moore, & Almeida, 2018; Yehuda et al., 2015). For example, having a CUD was associated with a history of PTSD, as well as deviant behaviour (as perceived by peers), male gender and being an offspring of a father with an SUD (Cornelius et al., 2010). There is currently little evidence available evaluating whether cannabis use might predispose someone to develop PTSD if they experience a traumatic event. A small longitudinal study suggests that, among individuals who had experienced a traumatic event, regular cannabis use increased the likelihood of having PTSD symptoms later in life (at age 36), compared to individuals who had not used cannabis at all (Lee, Brook, Finch, & Brook, 2018).

A large body of research has examined the effects of cannabis use on the alleviation or exacerbation of symptoms of PTSD (see Haney & Evins, 2016). Research in animal models suggests that cannabis and its constituents could offer therapeutic benefits to patients with PTSD (Loflin, Babson, & Bonn Miller, 2017; Bitencourt & Takahashi, 2018). Generalization of findings from animal studies should be made with caution since the endocannabinoid system is quite different in animals than in humans. Many individuals with PTSD report using cannabis to cope with their symptoms (Bonn Miller, Babson, & Vandrey, 2014; Bonn Miller et al., 2012; Cogle, Bonn Miller, Vujanovic, Zvolensky, & Hawkins, 2011). Evidence from observational studies indicates that cannabis use among patients with PTSD is actually associated with poorer mental health outcomes, including increased symptom severity (Gentes et al., 2016; Manhapra, Stefanovics, & Rosenheck, 2015; Wilkinson, Stefanovics, & Rosenheck, 2015) and suicidal ideation (Johnson et al., 2016; Manhapra et al., 2015; Wilkinson et al., 2015). However, there is a lack of longitudinal studies controlling for previous cannabis use and baseline symptom severity, as well as blinded, randomized and placebo-controlled studies in patients with PTSD, to assess the impact of cannabis use on the course

or symptoms of PTSD. There are two ongoing clinical trials examining the effects of cannabis with varying THC and CBD content on PTSD symptoms (Bonn Miller, 2019; Eades, 2019). In addition, a recent study conducted among male, Canadian military personnel on the therapeutic potential of the synthetic cannabinoid nabilone suggests that it could be a clinically relevant treatment to improve trauma-related nightmares (Jetly, Heber, Fraser, & Boisvert, 2015).

There is a lack of research examining the effect of sex and gender differences on the association between cannabis use and PTSD. Gender itself is an important risk factor for developing PTSD, with females much more likely to develop PTSD over their lifetime compared with males (Olf, 2017; Van Ameringen, Mancini, Patterson, & Boyle, 2008). In addition, different forms of trauma contribute to the development of PTSD among males and females (Van Ameringen et al., 2008). Importantly, males and females have differences in cannabinoid receptor levels and pharmacology that might influence the effects of cannabis on PTSD outcomes. Females have higher CB1 receptor levels under basal, non-stress conditions and PTSD results in significantly higher levels in females but not males (relative to healthy, trauma-free controls) (Neumeister et al., 2013). Given that there are important sex and gender differences for both cannabis use and PTSD, future research on the association of cannabis use and PTSD should consider both sex and gender variables.

## Suicidal Behaviours

Suicide is death caused by self-directed behaviour that is intended to result in death. Suicidal behaviours include suicide ideation and suicide attempts. A suicide attempt is defined as a non-fatal but deliberate, self-destructive behaviour with an intent to die because of the behaviour. Suicidal ideation is defined as thinking about, considering or planning suicide. Although suicide ideation is a risk factor for suicide attempts, most individuals who have suicidal thoughts will not necessarily make attempts at suicide (Franklin et al., 2017; Freeman et al., 2017).

Several mental illnesses, including schizophrenia (Hor & Taylor, 2010), depression (Hawton, Casañas i Comabella, Haw, & Saunders, 2013) and PTSD (Krysinska & Lester, 2010), are associated with increased risk for suicidal behaviours. Given that cannabis use and CUD link to mental disorders, it is not surprising that cannabis use is associated with suicidal behaviours. Additional genetic and environmental risk factors underlie the association between

cannabis use and suicidal behaviours, including family history (Qin, Agerbo, & Mortensen, 2002), early childhood trauma (Dube et al., 2001) and having an SUD (Schneider, 2009). Evidence suggests that cannabis use, especially heavy and frequent use, is also an important risk factor contributing to the likelihood of suicidal behaviours (i.e., completed suicide, suicide attempts and ideation) (Borges, Bagge, & Orozco, 2016; Delforterie et al., 2015; Lynskey et al., 2004; Shalit, Shoval, Shlosberg, Feingold, & Lev-Ran, 2016).

A recent systematic review concluded that, even in the absence of any premorbid suicidal behaviours, cannabis use during adolescence was associated with increased risk of suicide ideation and attempts (Gobbi et al., 2019). This conclusion is consistent with other primary studies (Delforterie et al., 2015; Kung, Pearson, & Liu, 2003; Kung, Pearson, & Wei, 2005; Moore et al., 2007; Shalit et al., 2016) and systematic reviews (Borges et al., 2016) reporting an increased risk of suicidal behaviours among both adolescents and young adults who have frequently used cannabis. Of note, some studies might underestimate the association of cannabis use with suicide because these behaviours are embedded within the assessment of depressive disorders (i.e., suicide ideation is a symptom of depression) (Shalit et al., 2016).

As is the case for mental illness, suicide ideation and attempts are dependent on sex and gender, and this influences the relationship between cannabis use and suicide behaviour. Females are generally at a higher risk for suicidal ideation and attempts, while males have higher rates of suicide completion (Nock et al., 2008; Turecki & Brent, 2016). There is evidence that the association between cannabis use and the incidence of suicide ideation is significant only in males, while the initiation of cannabis use at all is associated with increased suicide ideation in females (Shalit et al., 2016). This evidence is consistent with another report that there was a significantly increased risk of suicide ideation in males who used cannabis, but not in females (van Ours, Williams, Fergusson, & Horwood, 2013).

## Conclusions and Implications

The evidence in this report clearly illustrates the high prevalence of comorbidity between regular cannabis use and mental illness. This comorbidity does not mean that one causes the other, and establishing causality or directionality is difficult for many reasons. Three main scenarios contribute to the comorbidity between cannabis use and mental illness and the evidence for each scenario varies for different mental disorders. One scenario is that cannabis use increases the risk for mental illness. This scenario is especially true for psychosis and schizophrenia, and to a lesser extent for

depression. Second, some mental disorders themselves might increase the risk for regular cannabis use. For instance, social anxiety disorder might increase the risk for developing problematic cannabis use. The third scenario is that cannabis use and mental illness are both influenced by overlapping genetic and environmental factors.

An important conclusion from this review is that regular cannabis use, independent of other risk factors and premorbid conditions, does increase the risk for developing several mental conditions. However, an equal emphasis should be placed on the fact that most individuals who use cannabis do not go on to develop a mental illness and that most individuals experiencing mental illness do use cannabis. From this perspective, a primary recommendation of this review is for further research into the contribution of individual differences into these complex relationships.

A substantial amount of research indicates that regular cannabis use increases the risk for developing schizophrenia in a dose-dependent manner. While this risk is pronounced among individuals with genetic susceptibility to psychosis and schizophrenia, the relative risk of psychosis remains even among individuals without pre-existing vulnerability. Public health messaging materials should more clearly highlight this finding. The role that early initiation of cannabis use — defined as before the age of 17 — plays in increasing risk for psychotic disorders is another key public health message to highlight (Casadio et al., 2011; Malone et al., 2010). Adolescents who use cannabis are at greatest risk because the effects of regular cannabis use are more likely to be long lasting and persistent in the developing brain, which continues to develop until about the age of 25 (George & Vaccarino, 2015; Lorenzetti, Solowij, & Yücel, 2016). This finding also demonstrates that effective approaches are needed to delay the initiation of use and reduce the frequency of use among youth. Similarly, there is a need to increase the capacity of those who work with youth by providing them evidence-informed tools and resources (Fleming & McKiernan, 2018).

In the general population, the risk of developing mood and anxiety disorders appears not to increase as a result of using cannabis, especially after the use of alcohol and other substances are taken into account. From a public health perspective, this means that most individuals who use cannabis will not go on to develop clinically significant symptoms of depression or anxiety. Instead, the occurrence of depression or anxiety among individuals who use cannabis, particularly those who use it often, might be related to difficulties with other substances, the presence of chronic and ongoing stressors, early life adversity, and low socioeconomic status, among other factors. However,

it is extremely important to distinguish between population-level risk and risk at the level of the individual. While the risk of developing mood and anxiety disorders among the general population is relatively low, there is limited research examining how individual differences, including genetic, social and environmental differences, interact with cannabis use in promoting or preventing the evolution of depressive and anxiety disorders.

The impact of cannabis use on mental health outcomes varies among individuals and across different disorders. As an example, one individual's cannabis use might be associated with minimal risk for psychosis or schizophrenia, but instead significantly increases their risk of developing depression or an anxiety disorder. For another individual, the combination of risk factors across mental disorders might differ. Accordingly, it is important that individuals using cannabis or considering initiating cannabis use consider the overall risk as a whole of developing any mental illness rather than the risk for a specific mental illness. Indeed, this overall risk should be a central public education message. Meanwhile, further research needs to focus on how individual differences promote the emergence and persistence of mental illnesses to inform individuals of their vulnerability to developing various mental health outcomes, and to promote approaches for reducing levels of risk, including but not limited to abstinence. This research includes further examining how sex and gender interact with cannabis use in relation to mental illnesses.

These are important conclusions given that a significant proportion of Canadians aged 15 or older (almost 16% or about 4.6 million individuals) report using cannabis at least once in the past three months (Health Canada, 2018). There are still many misconceptions about the effects of cannabis on health, particularly among youth (Hall & Morley, 2015; McKiernan & Fleming, 2017; Wadsworth & Hammond, 2019). Cannabis is commonly used for the symptom management of mental disorders, and healthcare providers are authorizing cannabis use for mental disorders (Smith et al., 2019; Turna, Simpson, Patterson, Lucas, & Van Ameringen, 2019). These observations are concerning because there is currently no strong evidence to support the use of cannabis for most mental health conditions (National Academies of Sciences, Engineering, and Medicine, 2017). Rather, the evidence indicates that regular cannabis use contributes to poorer mental health outcomes over time,

and significantly increases the risk of developing a CUD among individuals with mental illness. It is, therefore, important that individuals, including healthcare providers and policy makers, are well informed of the mental health risks associated with regular cannabis use, and of strategies to reduce those risks (Fischer et al., 2017).

There has been a lot of interest among researchers, policy makers and the general population in whether cannabis use causes mental illness, but much less attention has been paid to whether mental illness leads to cannabis use. Although cannabis use is more prevalent among individuals with mental illness, the majority of individuals with depression, anxiety and PTSD do not use cannabis. Nevertheless, individuals with mental illness are considerably more likely to develop problematic cannabis use behaviours and a CUD. These findings need to be more effectively disseminated to individuals with a mental illness or at risk of developing a mental illness, as well as healthcare practitioners who are considering authorizing cannabis use for mental health issues. These findings are especially important for youth given that mental illnesses typically emerge in adolescence and early adulthood. Therefore, a key takeaway from this review is the need to develop targeted educational materials informing those with mental health concerns about the increased risks associated with cannabis use and mechanisms to reduce these risks, such as the lower-risk cannabis use guidelines (Fischer et al., 2017), as well as treatment services.

This report highlights the gaps in our understanding of the cause and effect relationship between cannabis use and mental health outcomes. Unlike alcohol where there are public health and research standards for what constitutes heavy or regular use, there is no single definition in the scientific literature as to what constitutes regular cannabis use. Differences among studies for how regular cannabis use is assessed not only affect the mental health outcomes measured, but also add to the variability of these measured outcomes among studies. Differences in frequency, dose and strains of cannabis among studies further add to the complexity of cannabis effects on the development and trajectory of mental illness. Consistency for how cannabis use is measured and for what qualifies as heavy or regular use will improve studies examining the link between cannabis use and mental illness.

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