Review Paper

Cannabinoids in Mental Health – A Problem or a Solution?

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ABSTRACT

Cannabis use in Canada has increased steadily since legalization, with recent data indicating widespread usage. While cannabis has been used for recreation and medicinal purposes for decades, concerns arise regarding its potential adverse effects, particularly psychosis in young individuals. Awareness of these effects is crucial for informed decision-making and prevention of negative outcomes. This literature review aims to analyze the available literature and identify the impact of cannabis usage on mental health and psychiatric illnesses. The available literature highlights the impact of cannabis use on neuropsychiatric health, cognition, and mental wellness, in addition to contextualizing this following the legalization of cannabis in Canada. The research describes the diverse forms and potencies of cannabis and underscores the need for cautious consumption due to its potent effects, particularly when inhaled. The prevalence of cannabis use, particularly among adolescents, is also a cause for concern, with evidence indicating the associated risks to brain development and development of psychotic disorders in this population. A central focus identified is the relationship between cannabis use and neuropsychiatric disorders, notably psychosis, with evidence pointing to a dose-response relationship and heightened risk among heavy and early users, especially those predisposed to mental health issues. Moreover, the results of this review emphasize the impact of cannabis potency and the heightened risk associated with high-potency variants like skunk, especially with frequent use. It also delves into the therapeutic potential of cannabinoids like THC and CBD, underlining the need for careful consideration in medical applications. Beyond psychosis, we also identified cannabis's broader impact on mental health, including associations with depression, anxiety, and cognitive impairments, and the importance of considering medication compliance, particularly in psychiatric populations. The risks of cannabis use on fertility and pregnancy outcomes were also evident. While acknowledging cannabis's therapeutic potential, this literature review elucidates the need for public health interventions to mitigate its negative effects, including educational initiatives, policy reforms, and interventions for cannabis use disorder. It serves as a valuable resource for policymakers, healthcare practitioners, and researchers navigating the complexities of cannabis use and mental health, offering insights into future research directions and public health strategies.
Keywords: cannabis, cannabinoids, mental health, THC.

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INTRODUCTION

Cannabis is a substance that has been recently legalized in Canada and has been used for leisure and as a remedy by different cultures for decades [1]. Its impact on the mind and body have been investigated over many years. The legalization of cannabis in Canada has brought about economic implications, including costs and potential adverse outcomes. Despite the economic benefits such as tax revenue generation and job creation, there are also substantial costs associated with regulation, enforcement, and public health interventions. For instance, a study by the Canadian Centre on Substance Use and Addiction estimated that the societal costs of cannabis use in Canada amounted to approximately $2.8 billion in 2017, encompassing

healthcare, criminal justice, and productivity losses [2]. Moreover, concerns persist regarding the potential increase in cannabis-related health issues, including cannabis use disorder, cannabis related psychosis and impaired driving incidents. Statistics Canada reported a 43% increase in cannabis-impaired driving incidents following legalization in 2018, highlighting the need for ongoing monitoring and intervention strategies [3].

Various forms of cannabis are available, including concentrates like shatter, which are highly potent extracts typically consumed through vaporization or dabbing methods [4]. Potency levels of cannabis products can vary widely, with some strains containing higher concentrations of psychoactive compounds like THC, leading to stronger effects [5]. Different strains of cannabis offer diverse cannabinoid profiles and effects, catering to various preferences and medical needs [6]. Though, purchasing cannabis products from unregulated sources, such as reserves, poses risks due to the lack of quality control and potential contamination with harmful substances [7].

The Global Burden of Disease study in 2010 discovered that 13.1 million individuals depended on cannabis, with a point prevalence of 0.19%. [8]. Since its legalization in 2018, cannabis use in Canada has steadily increased with recent data indicating that approximately 27% of Canadians aged 15 and older, equivalent to over 10 million individuals, used cannabis in the past year [9]. Age of use and a dose response relationship has been considered as a possible cause of psychosis in young individuals. As cannabis has been legalized in Canada the public should be wary of its possible negative effects and consequences to prevent adverse outcomes and for the public to make an informed decision before consuming this substance.

Understanding Cannabis and Neuropsychiatric Implications

The brain is vulnerable to external factors including substance use especially in the early years of development. The consumption of cannabis among children and adolescents in North America, including Canada, has become a growing concern in recent years. Statistics from the Canadian Cannabis Survey reveal that approximately 19% of youth aged 15 to 19 reported using cannabis in the past three months, with rates of use increasing with age [9]. Such early onset of cannabis use can have significant implications for brain development. Chronic cannabis use during adolescence has been associated with alterations in the basal ganglia, which are involved in motor control and reward processing [10]. Additionally, the hippocampus, crucial for memory and learning, may be adversely affected by cannabis use during adolescence, leading to impairments in cognitive functions [10]. Furthermore, the cerebellum, responsible for coordination and motor control, can also be impacted by cannabis use, potentially leading to disruptions in motor skills and balance [11].

A lesser-known fact is that the corpus collosum which is responsible for behavior and communication, is the final maturing part of the brain and it does not completely develop until individuals reach their mid-twenties [12]. This advises that the brain remains susceptible to damage even during the teenage and young adult years by a variety of factors including substance use. Semple and others [13] supplement that due to this, young individuals' brains could have a greater vulnerability to the negative consequences of cannabis on the mind. Caspi and his team [14] completed a longitudinal exploration of eight hundred adolescent cannabis users which established that in those that used cannabis there was a polymorphism in the catechol-O-methyltransferase (COMT) gene. The authors found that this polymorphism was associated with later onset of psychosis.

We know that dopamine plays a role in psychosis and potentiating the positive symptoms of psychosis. Antipsychotic medications exert its effects on the dopamine system, decreasing its effects. It has been observed that tetrahydrocannabinol (THC) a main element of cannabis increases mesolimbic dopaminergic activity, which increases overall dopamine availability in the brain. THC was uncovered to have a link to positive symptoms of psychosis [15]. Cannabis works on the CB1 and CB2 receptors, CB1 is known to reduce the uptake of dopamine therefore increasing its action [15]. CB1 and CB2 have been found to have a role in the basal ganglia so researchers have investigated the role of cannabis in neurodegenerative diseases [15]. Nevertheless, evidence of the benefits of cannabis on medical conditions such as anorexia, Alzheimer's, dementia, and Huntington's are faint and indeterminate [16]. Since cannabis works by increasing dopamine in the brain it should come as no surprise that it would affect the positive symptoms of psychosis.

Most interestingly, cannabis also exercises its effects on the mind in manipulating EEG and brain wave activity. Campbell [17] looked at thirteen patients aged sixteen to twenty-two who had used cannabis and no other illicit drugs. In those who used cannabis and sought psychiatric help they noticed that these individuals had an excess of sharp and theta wave activity on their EEGs especially in the temporal and frontal part of the brain. In those who used cannabis and sought psychiatric help ten of the eleven EEGs were abnormal. In those who consumed cannabis without the need for psychiatric assessment 8 of the 11 EEGs were abnormal. This has been especially noted in those individuals who later become psychotic. This is concerning as clearly cannabis has an influence on brain activity. It has been that chronic cannabis consumption leads to cognitive impairments especially in attention and memory [18].

The Influence of Age

Longitudinal studies have revealed that cannabis use during adolescence and young adulthood particularly among individuals under 25 years old, is linked to specific deficits in cognitive domains. For instance, heavy cannabis use in this age group has been associated with impairments in attention, manifested by reduced ability to sustain focus and increased distractibility [19]. Moreover, cannabis use during critical developmental periods can detrimentally affect problem-solving abilities and judgment, leading to difficulties in adapting to novel situations and making sound decisions [20]. Learning abilities are also compromised, with cannabis users demonstrating diminished capacity to acquire and retain new information, potentially hindering academic and occupational performance [10]. Additionally, cannabis use in adolescence and young adulthood has been correlated with specific deficits in memory, including impaired episodic memory retrieval and recognition [21]. Visuospatial abilities, such as spatial orientation and navigation, may also be compromised in cannabis users, affecting tasks requiring mental manipulation of spatial information [21]. Overall intelligence, encompassing aspects like psychomotor speed and manual dexterity, may exhibit decrements in individuals with a history of cannabis use during adolescence and young adulthood, impacting various facets of daily functioning [22].

Younger age at onset of cannabis use is also a significant risk factor for developing psychosis in adolescents with a predisposition to mental health diagnoses including psychosis compared to using cannabis in any other age group [23]. Consumption of cannabis prior to eighteen years old seems to have the ultimate negative effects. It has been found that in adolescents' cannabis can elicit psychotic symptoms specifically in those who have a predisposition for psychosis [24]. This was reinforced by another study which showed that in those who used cannabis prior to eighteen years old, those individuals had a greater risk of receiving a diagnosis of schizophrenia in the following fifteen years [25]. Andreasson and others [26] established that in those who smoked cannabis preceding age eighteen had a 2.4 x bigger risk of being diagnosed with schizophrenia compared to those who had never used cannabis. In fact, a dose-response relationship between cannabis uses prior to the age of 16 and the incidence of schizophrenia by age 45 was established in the Swedish Conscript Study, with a 3-fold increase in risk reported in those using cannabis more than 50 times prior to the age of 18 years [26-27]. Studies have unearthed that the age of psychosis including schizophrenia for persons who used cannabis was on average 2.70 years earlier before nonusers. and the development of a psychotic disorder has been established [28]. Myles and others also agreed that the mean age of psychosis amongst those that used cannabis was three years earlier than those who did not use cannabis. These authors divulged that in those who used cannabis, psychosis age of onset was 32 months earlier than those who did not use cannabis ($p<0.001$) [29]. Contrary to these results, authors in their meta-analysis discovered that those who used cannabis prior to age seventeen had enhanced cognitive functioning compared to those who used cannabis after sixteen years old. Most research points to a clear link between earlier age of use with cannabis and an increased risk of psychosis. This is very concerning because healthy years of life prior to psychosis are reduced by usage of cannabis [30].

Stefanis and others [31] piloted a cross-sectional survey during a continuing cohort study of 3500 nineteen-year-old individuals in Greece. Individuals filled out a forty item Community Assessment of Psychic Experiences measuring aspects of positive and negative dimensions of psychosis. Prevalence of cannabis use was 6% compared to other drugs at 1%. The authors found an association with positive and negative aspects of psychosis in those who used cannabis. Those who used cannabis prior to sixteen years old had a greater effect than those who used cannabis after fifteen years old independent of frequency of use. In the two

hundred individuals who used cannabis 26% had used it first prior to 15 years old compared to other drugs which were at 1%. It was found that females were less likely to use cannabis [31].

Dose Dependance and Potency

How much cannabis is too much? There appears to be a strong relationship between not only when cannabis is used in adolescence but also how much and in what potency that determines negative health outcomes. Oral ingestion of cannabis results in delayed onset of effects and increased variability in potency due to the unpredictable nature of absorption in the digestive system [32]. Conversely, inhalation delivers cannabinoids directly to the bloodstream via the lungs, leading to rapid onset of effects and more precise control over dosage [32]. Studies have indicated that inhaled cannabis tends to have a higher bioavailability and a more consistent potency profile compared to oral ingestion [33-34].

It has been found that the effects of THC were dose specific. Their study uncovered that in persons who had 2.5 to 5 mg of IV THC had recall deficits compared to those individuals with no THC in their system. The dose dependent relationship was revealed when those who had 5 mg did worse with cognitive performance compared to those who had 2.5 mg [15]. Maconi and others [35] also confirmed a dose response relationship in noting a fourfold increase in the heaviest cannabis users and a twofold increase in those who are average users. High potency cannabis was shown to have the most severe effects of mental health [36]. Hall and Degenhardt [25] agreed that if a system of cannabis psychosis existed it would have to be associated with potency and high doses of THC. Semple and others conducted a meta-analysis which decided a dose relationship was seen especially in vulnerable groups including adolescents and those with a genetic risk of schizophrenia [13]. Kraan [37] looked at seven prospective studies. They found that cannabis use was only predictive of psychosis in those who were abusing or dependent on cannabis. They also noted a dose response relationship. Though the exact dosage threshold varies depending on factors such as potency, frequency of use, and individual susceptibility [38].

Frequency of usage is also another variable in growing the chance of negative health outcomes. It was found that those who used cannabis anywhere from one to ten times had a 1.3 x risk of evolving into a diagnosis of schizophrenia. According to Ortiz-Medina and others [39], regular cannabis consumption increases the likelihood of developing a persistent psychotic disorder by at least two-fold. In those who had used cannabis between one to fifty times had a three times greater risk and those who smoked cannabis over fifty times had a risk of six times higher. McGrath and others [40] in their sibling pair analysis found that the longer duration of cannabis use led to a higher risk of psychosis. In fact, they found that those who started using cannabis around 15 years old and for more than six years had twice the risk of developing psychosis. Moore and others [41] found that there was a dose response effect with those who used cannabis frequently (2.09, 1.54–2.84). More frequent use resulted in a 50-200% increase in risk. The authors note that cannabis increases psychosis by about 1.4 x. The authors believe that 14% of psychosis in young individuals in the UK could have been prevented if there were no cannabis consumption.

Di Forti and others [42] looked at the use of skunk-like (high-potency) cannabis in London and how it affected cannabis psychosis in 410 individuals aged 18-65. They found a threefold increase in psychosis in those who used skunk cannabis compared to controls (adjusted odds ratio [OR] 2.92, 95% CI 1.52–3.45, p=0.001). In their study they found the greatest risk in those who used cannabis every day and those who used the high potency skunk cannabis. A first episode of psychosis was more likely in those who used cannabis at 15 years old or younger. In those that used skunk cannabis once a week their risk of a psychotic episode was twice as high (p=0.020) and if thy used it on weekends the risk was three times greater (p=0.008) [42]. If they were daily users, their risk of a psychotic disorder was five times as high (p=0.001). The authors determined if causality was established 19.3% of psychotic disorders were due to daily cannabis use (95% CI 1.91–7.76),). If causality between skunk cannabis was found, then skunk was found to be the greatest cause for new cases of psychosis (24%). The authors concluded that daily use of high potency cannabis was the most predictive of a diagnosis of psychotic disorders. This correlation was found to be greater than either frequency or potency [42].

Cannabis and Psychosis

Cannabis use is an independent risk factor for the development of persistent psychotic disorders, particularly in those at genetic risk for developing schizophrenia and those who previously experienced psychotic symptoms [13]. It is also known that cannabis use has led to the earlier diagnosis of schizophrenia by 2.7 years [43]. Even when controlling for prodromal symptoms and family history, cannabis use remained a significant risk factor [44].

Following cannabis consumption, CB1 receptors that control the dopaminergic neurons are activated by THC. Once dopamine is released, it binds to the dopamine receptor subtypes (DAT1-DAT5). DAT1 polymorphism increases risk of psychosis with cannabis abuse [45]. Heritable variations in dopamine neurotransmission affecting the signaling cascade or synaptic availability of dopamine moderate sensitivity to the acute and long-term effects of cannabis on psychosis suggest that individuals carrying the risk variants of either the DAT1 3′UTR VNTR or the AKT1 rs130233 polymorphisms have an increased sensitivity to the psychotic effects of δ-9-THC. However, this is especially increased in subjects who carry both these variants [46].

Many studies have found a causal link between cannabis and psychosis even when controlling for confounders. Starzer and others [47] found that 47% of individuals experiencing a cannabis-induced psychotic episode progressed to develop a primary psychosis, compared to 30% of those with amphetamine-induced psychosis. The Swedish Conscript Study revealed a dose-response correlation between cannabis use before the age of 18 and the onset of schizophrenia by age 45, indicating a three-fold rise in risk among individuals who reported consuming cannabis more than 50 times during adolescence. Spencer [48] stated that cannabis acts as a precipitating element in those individuals who are predisposed to psychosis and that some element of the drug has a toxic effect on an individual's brain. Carney and others [36] completed a meta-analysis using thirty studies in which they looked at individuals who were at high risk for psychosis. They then tried to determine if using cannabis worsened outcomes regarding an individual's journey with psychosis. It was found that in those who were considered high risk for psychosis, 26.7% of individuals were current users of cannabis, 52.8% were lifetime users and 12.8% had Cannabis Use Disorder. Those who were cannabis users had increased rates of unusual thought content and suspiciousness. Those who were cannabis users experienced more severe positive symptoms of psychosis [36].

Ultra-high-risk individuals (who are identified as individuals with a greater predisposition to a conversion to full blown psychosis) were also more likely to have used cannabis during their life. It was also interesting that those who were considered high risk were more likely to have cannabis use disorder compared to the control. The authors did not find an association between cannabis and negative symptoms of psychosis. This was supported by Andreasson and others [26] who noted that those who used cannabis had more positive psychosis and an abrupt onset of schizophrenia compared to those who did not use cannabis. Research by Lange and others [43] in their meta-analysis show also showed a relationship between cannabis and early psychosis. Maconi and others [35] in their meta-analysis of 10 studies found that increased levels of cannabis was associated with an odds ratio of 3.90 (95% CI 2.84-5.34) of developing psychosis or schizophrenia. In those that have used cannabis. Moore and his team [41] found that psychosis was an outcome (adjusted OR 1.42, 95% CI 1.20–1.65). The authors found that there was an increase in psychosis of about 40% in those who had used cannabis. Furthermore, Ortiz-Medina and others [39] reported that regular cannabis use at least doubles the risk of developing a chronic psychotic disorder.

Degenhardt and Hall [25] found that cannabis increases relapse and can precipitate psychosis. Hasan and others [49] mirrored these findings and observed that cannabis use was associated with increased relapse rates, more hospitalizations and pronounced positive symptoms in psychotic patients. Moreover 47% of individuals with a cannabis induced psychotic episode go on to develop a primary psychosis, compared to amphetamines where 30% convert. Amar and Potvin [50] recognized three epidemiological studies that acknowledged a link between cannabis use and psychosis and five articles which addressed that chronic use of cannabis increased the incidence of psychosis symptoms but had no role in an established psychosis diagnosis. The authors concluded that cannabis increased the risk of psychosis in those that are determined to be already vulnerable, young heavy users and those who are predisposed to psychosis.

So, what happens when cannabis use is stopped? Chopra and Smith [51] looked at 200 patients that entered a psychiatric hospital in Calcutta India between 1963 to 1968. They studied individuals who experienced psychotic symptoms after cannabis use. These individuals experienced symptoms which included: confusion, delusions, mostly visual hallucinations, emotional lability, amnesia, disorientation, depersonalization, and paranoia. One third of the patients had no prior psychiatric history. What is most interesting is that after ceasing cannabis use, all experienced symptoms which remitted in days to weeks showing a strong relationship between cannabis and psychosis. This shows the potential benefits of ceasing cannabis use in potentially reducing the symptoms and experiences of psychosis.

Additional Psychiatric Implications

Cannabis is known to be a contributing factor to the development of psychotic conditions including schizophrenia. The use of cannabis can lead to both addiction and dependence on this drug which has negative outcomes [52]. Chronic cannabis use is associated with an increased risk of mental health issues which include anxiety and depression and suicidality especially in young adults [53]. Gibbs and others [54] investigated the association between cannabis and the incidence of manic symptoms. The authors conducted a systematic review, and six articles met inclusion criteria. 2391 individuals were surveyed. It was found that cannabis use exacerbated manic symptoms in those who were diagnosed with bipolar disorder. The authors referred to a study by Henquet and others [24] that cannabis was associated with a threefold risk (OR 2.97, 95% CI 1.80-4.90) of risk of a new onset of mania. Lev-Ran and others [55] found that in those with diagnosed bipolar disorder rates of cannabis use disorder was 7.2% compared to 1.2% of the general population. After adjusting for other variables those with bipolar disorder and CUD were found to be at an increased risk for nicotine dependence (67%), alcohol (66%) and other drug disorders (71%) and antisocial personality disorder (three times greater) compared to controls. In those who have CUD the onset of bipolar disorder was earlier. Episodes of manic, hypomanic and depressive episodes were greater than controls. There was no association found between suicide and cannabis use. Gobbi [53] noted that cannabis consumption leads to an increased risk of numerous mental health conditions including depression, anxiety, and psychosis. Cannabis is linked to an increase in cognitive impairments especially in memory and attention [56].

Therapeutic effects of Cannabis: Is It Ever Helpful?

Whiting and others [57] looked at randomized clinical trials and found 79 trials investigating the role of cannabinoids in treating nausea and vomiting due to chemotherapy, appetite stimulation of those with HIV/AIDS, chronic pain, spasticity in those with multiple sclerosis, glaucoma, Tourette's and sleep disorders. Although they found some improvement in experienced symptoms no true statistical significance was achieved. Compared with placebo there was a benefit of decreased nausea and vomiting in: (47% vs 20%; odds ratio [OR], 3.82 [95% CI, 1.55-9.42]; 3 trials), decreased pain (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials) and reduction in spasticity (95% CI, −0.24 to 0.01]; 5 trials). However, these individuals also had side effects of dizziness, nausea, dry mouth, somnolence, fatigue, vomiting, disorientation, drowsiness, and hallucinations. There was moderate evidence for the use of cannabis in neuropathic or cancer pain and spasticity for MS. There was low quality evidence for nausea and vomiting due to chemotherapy, appetite stimulation in HIV, sleep disorders, and Tourette's. Wilkinson and others [58] agreed to suggest cannabis for PTSD, Tourette's, agitation and Alzheimer's was of low quality. Andrade [59] quoted that in terms of chemotherapy nausea, pain and spasticity only modest benefits were noted. Inconclusive benefits were found in terms of increasing appetite, reducing tics, and improving mood. This really points to the fact that cannabis has a very limited role in treating medical conditions. Side effects are present and can be debilitating especially if individuals experience disorientation and hallucinations.

One small study did find therapeutic benefits of cannabis. A study of 94 individuals in Hawaii found that cannabis was beneficial in the management of chronic pain, insomnia, and anxiety [60]. Average pre-treatment pain was high at 7.8 and post treatment was 2.8 at a decrease of 64%. Reduction of anxiety (by 50%) decreased nausea (10%) increased concentration (9%) and decreased depression (7%). In patient notes that were presented individuals noted a decreased need for other pain and anxiety medications. It appears that in some select groups of individuals cannabis can be beneficial.

THC vs Cannabidiol (CBD)

Iseger and Bossong [61] noted that THC has psychotic properties, but the plant derived cannabidiol (CBD) may have antipsychotic benefits. CBD is known to cause fewer delusions and hallucinations. The researchers note that CBD can act in opposition towards psychotic symptoms and reduce the cognitive deficits caused by THC administration [61]. Zlebnik and others [62] found that cannabidiol was not psychoactive and it does not influence the cannabinoid type 1 (CB1) receptor. Cannabidiol was found to reduce the effects of amotivation via action on the $5HT_{1A}$ receptor. These results point to potential treatment benefits of cannabinoids. The authors also mention the role of CBD in neurogenesis. Since cannabis plays a role in psychosis there is a possibility of pharmacological treatments targeted towards the endo-cannabinoid receptors [29].

Medical Side effects and Adverse Outcomes

Acute use of cannabis has side effects such as dry mouth, dizziness, fatigue, and headache [16]. Kedzior and Laeber [63] looked at 31 studies from 10 different countries. They found that cannabis was counter to popular belief associated with anxiety after adjusting for any confounders (OR 1.28, 95 % CI 1.06-1.54, P=0.01). It turns out that some anxiety relief can be achieved with minimal consumption and low dose cannabis, but heavier doses and regular usage can lead to cannabis use disorders and increased anxiety. This was true when controlling demographics and other illicit substances. Driving after cannabis use is known to increase accidents on the road [59]. Potential adverse effects include addiction, dependence, psychosis, and cognitive issues [58]. In terms of pregnancy, it can cause fetal growth restrictions and can affect adolescent neurodevelopment. It can lead to psychosis and possibly cancer [59]. Whiting and others [57] noted that cannabis is associated with adverse effects compared to placebo treatments. The exception was with dronabinol. The authors noted side effects of dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, diarrhea and disorientation, hallucinations, and confusion. The highest ORs were for dizziness, euphoria, disorientation, and confusion. Walsh and others [64] identified 31 studies with a total of 23,850 individuals that suggest that cannabis for therapeutic purposes could be problematic in those with psychosis. 65]Cannabis use has been associated with adverse effects on sperm quality, including decreased sperm count and motility, as well as alterations in sperm morphology [65]. Cannabis use during pregnancy has been associated with adverse pregnancy outcomes and infant health complications. Exposure to cannabis during pregnancy may lead to lower birth weight, preterm birth, and increased risk of stillbirth [66-67]. Moreover, maternal cannabis use during pregnancy has been linked to alterations in fetal brain development, potentially influencing long-term behavioral and emotional outcomes in offspring [68-69]. Infants exposed to cannabis in utero may experience neurodevelopmental deficits, including impaired cognitive function and attention problems later in life [70-71]. Prenatal cannabis use has been increasingly recognized as a potential risk factor for the development of neurodevelopmental disorders such as autism spectrum disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD). A large-scale prospective cohort study by Brown and others [72] found that prenatal cannabis exposure was linked to a higher likelihood of ADHD symptoms in children at the age of 10. Similarly, another longitudinal study conducted by Jensen and his team [73] revealed that maternal cannabis use during pregnancy was associated with an increased risk of ASD traits in offspring at the age of 6. These findings align with a meta-analysis by Corsi and others [74], which reported a pooled odds ratio indicating a positive association between prenatal cannabis exposure and the risk of neurodevelopmental disorders in children. Furthermore, a systematic review by Calvigioni and others [75] highlighted the potential neurobiological mechanisms through which prenatal cannabis exposure may contribute to the development of ASD and ADHD, including disruptions in neuronal development and neurotransmitter systems.

Cannabis also has negative effects on one's physical health and can contribute to respiratory problems that are like that of cigarettes and tobacco [76]. Cannabis smoke contains the same harmful chemicals found in tobacco smoke, such as tar and carcinogens. Chronic cannabis smoking has been associated with increased risk of bronchitis, chronic cough, and respiratory infections. Additionally, long-term cannabis use has been linked to decreased lung function and an increased risk of developing chronic obstructive pulmonary disease [76]. Chronic cannabis use has been linked to cannabinoid hyperemesis syndrome (CHS), characterized by recurrent episodes of severe nausea, vomiting, and abdominal pain, likely secondary to dysregulated

endocannabinoid system, leading to gastrointestinal disturbances [77]. Furthermore, while cannabis has been explored for its potential antiemetic properties, paradoxically, heavy or prolonged use may exacerbate symptoms of nausea and vomiting [78].

Cannabis use can also affect medication compliance. Foglia and others [79] looked at 15 observational studies. Cannabis is the most used illicit drug in those who suffer from psychosis. Their study found that in those who use cannabis nonadherence to medication including antipsychotic were greater compared to non-users (OR 2.46) The risk for non-adherence was only present in current users (OR 5.79) and this risk was not present in former users (OR 5.5) and non-users (OR 1.12). Prevalence of lifetime cannabis use was determined to be 18.9% in four studies and 13.9% in eight studies. In addition to the variety

Cannabis can also affect neurocognition and short-term memory. Bogarty and others [80] compared neurocognition in those aged 15 to 45 years old who smoked cannabis versus those who did not. Those that were cannabis positive presented with worse current and premorbid IQ, verbal learning, verbal working memory and motor inhibition compared to those who did not smoke cannabis. Those who were older in age performed worse on processing speed, verbal memory and sustained attention. They, however, did better verbal learning and fluency. The only domain in which those who were cannabis positive did better was in conceptual set shifting.

Confounders and other variables

Confounders of the association between cannabis and psychosis need to be addressed. There are many factors that could also lead to psychosis in conjunction with cannabis use. Some confounders include genetic predisposition and other neurodevelopmental factors. Consumption of other substances that are stimulants can also lead to psychosis although less so than cannabis. Many studies included were unable to account for or include other substances in their research therefore it may be hard to draw causations of cannabis use and psychosis when other illicit drugs could be a factor. We should also consider that cannabis could be laced with other drugs and in recent times synthetic cannabis has now become available. Amphetamines are known to be another drug in which those who use cannabis are also more likely to use and are known to cause psychotic episodes [25]. Spencer [48] agreed that marijuana could be contaminated with L.S.D. or some amphetamine and that this would affect a psychosis outcome. Alcohol and cocaine are substances that could also affect cognition in those who have schizophrenia and is possible confounder [30]. According to their research there is a neurotoxin in tobacco that is almost always also found in cannabis [81]. Another potential confounder is that males are dominant participants in these studies, and we know males are known to experience psychosis at an earlier age [29].

When controlling these factors, it was found that alcohol use was not found to be associated with an earlier onset of psychosis. After controlling for variables including behavior, low IQ, cigarettes, gender, age, ethnicity, education, and marital status Arsenault and others [82] still concluded that there was a link between cannabis and psychosis independent of confounders. Myles and others [29] found that cannabis influenced psychosis 32 months earlier and was two weeks later in tobacco users compared to those who did not smoke ($p=0.974$) the results from the study show that cannabis and psychosis is not the result of tobacco or other potential confounders.

McGrath and others [40] with their study on matched sibling cohorts were able to remove any genetic or environmental confounders in describing the relationship of cannabis and psychosis. They used sibling pair analysis to study 3801 subjects with 1806 males. They investigated the association between cannabis and psychosis. In those who smoked cannabis for greater than 6 years there was an increased risk of nonaffective psychosis (adjusted odds ratio, 2.2; 95% confidence interval, 1.1-4.5), a high score on Delusions Inventory score (adjusted odds ratio, 4.2; 95% confidence interval, 4.2-5.8), and hallucinations (adjusted odds ratio, 2.8; 95% confidence interval, 1.9-4.1).

Benefits of Discontinuing Cannabis

It appears that discontinuing cannabis can cease a potential relapse into psychosis as well as put individuals at a lower risk of adverse health outcomes. Schoeler and others [83] found in 24 studies that showed that continued use of cannabis had a greater chance of relapsing into psychosis both in non-users (CI 0.22–0.50, $p<0.0001$) and discontinued users (0.12–0.44, $p=0.0005$). The authors also found that those who continued

to use cannabis had longer hospital admissions (CI, 0.13 to 0.58, p=0.02). It was found that continued use of cannabis led to an increase in positive symptoms of psychosis (95% CI 0.01 to 0.29, P=.05) increased relapse (p=0.04) and worsened level of functioning (p=0.008) but had no effect on experienced negative symptoms of psychosis (p=0.41). All these results were not shown in those who stopped using cannabis. This points to the suggestion that those who stop using cannabis can decrease their chances of relapse into psychosis. Arseneault and others [82] note in their five studies that there is a twofold risk between cannabis use and risk for schizophrenia. They estimate that cessation of cannabis use would reduce schizophrenia by 8%. The authors note that this is not a causational relationship but suggest cannabis use is one factor in a wide variety of factors leading to psychosis. From the above we can clearly see that even though cannabis can lead to adverse outcomes, discontinuing it can prevent some of these results.

Future Directions

Overall, those that are vulnerable to psychosis are those who use cannabis early and use a heavy amount of it [84]. In those that are vulnerable to psychosis early and heavy use of cannabis were correlated to psychosis. It is important to identify those who are considered 'high risk' for psychosis or adverse mental health outcomes. Some of these factors include those who are genetically susceptible, have another co-occurring mental health condition or those who also use other illicit substances. It is important to have public education to alert families about the risks of cannabis use to prevent such usage in young teens who are the most susceptible to the adverse effects of cannabis. Public policy needs to address these negative outcomes of cannabis use and alert the public to the possible dangers of cannabis use. Cannabinoid medications that have been approved by the FDA are dronabinol and nabilone. There is some evidence that cannabidiol and other forms of cannabis that are not psychogenic could play a potential role in treatment of diseases.

In those that require treatment of cannabis use disorder as well as co-existing mental health conditions it is important to approach care to these patients in a non-judgmental and non-confrontational way. Some evidence-based interventions include contingency management, pharmacotherapy like gabapentin, motivational interviewing (MI), and peer support. Contingency management involves providing rewards or incentives to individuals who abstain from cannabis use, thus reinforcing positive behaviors. Gabapentin, although primarily used for other conditions, has shown promise in reducing cannabis withdrawal symptoms and cravings [85]. Motivational interviewing aims to enhance an individual's motivation to change their cannabis use behavior by exploring ambivalence and increasing intrinsic motivation. Peer support, through group therapy or community-based programs, offers individuals a supportive environment and shared experiences to aid in recovery. Future areas of study may focus on the effectiveness of integrated treatment approaches, the development of novel pharmacotherapies, and the exploration of digital interventions for cannabis use disorder management [86].

CONCLUSIONS

The legalization of cannabis in Canada has sparked extensive research into its effects on mental and physical health. This literature review provides a comprehensive understanding of the available literature and underscores the complex relationship between cannabis use and psychiatric outcomes. Notably, cannabis consumption, particularly during adolescence, presents a significant risk factor for the development of psychotic disorders like schizophrenia. The potency and frequency of cannabis use further exacerbate adverse outcomes, with high-potency strains and heavy usage linked to increased risk of psychosis and cognitive impairments. Additionally, cessation of cannabis has shown promise in mitigating the risk of relapse into psychosis, highlighting the potential benefits of discontinuation interventions. On the physical health front, cannabis use mirrors the respiratory hazards of tobacco, contributing to chronic bronchitis and respiratory infections.

As research progresses, we must continue to explore the therapeutic potential of cannabinoids while elucidating their adverse effects. Clear public education and policies are crucial in informing individuals, especially adolescents, about the potential risks of cannabis use. Comprehensive care models that integrate substance use interventions with mental health treatment are vital for addressing the complex needs of individuals with cannabis use disorder and co-occurring psychiatric conditions. The emergence of

conditions, such as cannabinoid hyperemesis syndrome, further emphasize the future challenges and the diverse array of physical health risks associated with cannabis.

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