REVIEW ARTICLE

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Cannabis Use and its Association with Psychological Disorders

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ABSTRACT ~ ***Purpose of Review:*** *This is a comprehensive review of the association between cannabis use and psychological disorders. It reviews the latest and seminal evidence that is available and attempts to conclude the strength of such association.* ***Recent Findings:*** *Cannabis is a flowering plant with psychoactive properties, attributed to cannabinoids that naturally occur within the plant. These act through the CB1 and CB2 receptors to inhibit GABA and glutamate release, as well through other forms of neuromodulation through the modulation of the endocannabinoid system (eCBs); a system that is otherwise involved in different pathways, including reward, memory, learning, and pain. Recent societal changes have increased the use of both medical and recreational cannabis. Patients with mental illness are considered more vulnerable and are prone to reward-seeking behavior. Cannabis use disorder (CUD) has been shown to have an increased prevalence in individuals with mental illness, creating an explosive cocktail. Approximately 1 in 4 patients with schizophrenia are also diagnosed with CUD. Cannabis use is associated with 2–4 times the likelihood of developing psychosis in healthy individuals. It has also been associated with multiple poor prognostic factors in schizophrenia, as well as in patients with a history of psychosis who do not meet diagnostic criteria for schizophrenia. Cannabis has been linked with anxiety; THC has been shown to elicit anxiety; however, anxiety is also a trigger for cannabis use. However, a recent large meta-analysis did not find a convincing link between cannabis and anxiety. This was reiterated in a recent epidemiological study that did not find such a correlation; however, it did identify a link between cannabis use, substance disorder, alcohol use disorder, drug use disorder, and nicotine dependence. Similarly, contradicting data exists regarding the link of depression and cannabis use.*

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SUMMARY: *Cannabis use is increasing with recent societal shifts; however, its interaction with mental health is less well understood. CUD is highly prevalent in individuals with mental health disorders, especially those with other substance abuse disorders. There is evidence to support that cannabis use may trigger and worsen psychosis and schizophrenia. The link with depression and anxiety is less clear and needs further investigation. Personality disorder is linked with substance use disorder and shares similar risk factors with CUD.* Psychopharmacology Bulletin. *2020;50(2):56–67.*

Introduction

Cannabis is a genus of a flowering plant whose most well-known species include *Sativa*, *Indica*, and *ruderalis*.[1] In its dried flower bud form, it is referred to as marijuana.[1] Blocks of its plant resin are known as hashish.[1] Flavonoids, cannabinol, terpenoids, and cannabinoids are some of the bioactive molecules that dictate the qualities of different cannabis strains.[1,2] The relative proportions of cannabinoid varieties in a given strain determine psychoactive potency.[1] Of the nearly 100 types of cannabinoids, the two most well-known and clinically relevant are delta-9-tetrahydrocannabinol (THC), the principal psychoactive constituent of cannabis, and cannabidiol (CBD), an anti-inflammatory agent.[1] THC is a partial agonist of cannabinoid receptor 1 (CB1 receptor), while CBD is a CB1 receptor negative allosteric modulator.[3,4]

The mechanism of action by which cannabinoids exert their effects involves binding to G protein-coupled CB1 and CB2 receptors throughout the body, stimulating the endogenous cannabinoid system, altering levels of endocannabinoids (eCBs), and inhibiting the release of neurotransmitters like gamma-aminobutyric acid (GABA) and glutamate.[1,2] CB1 and CB2 receptors also allow for other forms of neuromodulation, including increased dopamine release, decreased acetylcholine release, and decreased norepinephrine release.[5] eCBs are endogenous neuroactive lipid messengers that play a role in reward, memory, learning, and pain pathways.[1] The highest concentrations of CB1 and CB2 receptors are found in the central nervous system and in immune cells, respectively.[1]

Societal and legal perceptions of cannabis have been shifting over recent years. Cannabis underwent national legalization in Canada in October 2018 and is experiencing a trend toward legalization in the United States.[6] In 2017, it was estimated that 43% of individuals ages 16–24 and 18% of individuals over 25 used cannabis in Canada.[6] Nationwide use of cannabis in the United States has increased from 5.8% of people age 12 or older in 2007 to 7.5% in 2013.[7] From what has been observed in Canada and in parts of the United States like Colorado and Washington, it is thought that with legalization comes

increased acceptance, reduced perception of risk, and increased use of cannabis by both adults and adolescents.[6] These anticipated trends make it essential to improve the current understanding of both the basic science and clinical applications of cannabis.[6]

To clearly outline the effects of cannabis on individuals with mental illness, it is essential to delve into the mechanism of action by which cannabis produces its physical and psychiatric effects. The "high" that is sought by most users of recreational cannabis is generated via the agonistic effects of THC on CB1 receptors.[6] The action of CBD somewhat opposes that of THC, having been shown by early studies to exhibit potentially therapeutic effects such as anxiolysis.[6] Different strains of cannabis have varying proportions of THC and CBD.[6] These proportions also vary by the preparation of cannabis such as resin, oil, or herbal and by the method of cultivation.[8] Over time, the strains most commonly used recreationally, both regulated and unregulated, have become characterized by high THC and low CBD potency.[6] The clinical effects of this proportion of THC and CBD can vary, in part due to the diffuse distribution of CB receptors throughout the brain and the variety of involved neurotransmitters, and can range from positive (relaxation, euphoria) to negative (anxiety, psychosis).[6]

Vulnerable populations, such as those with mental illness, are often characterized as having strong motives to seek short-term reward.[6] It has been shown that almost 60% of individuals with schizophrenia use illicit drugs.[2] With respect to cannabis, this short-term reward consists of the aforementioned feelings of relaxation and euphoria.[6] This association may explain why cannabis use disorder (CUD) is much more prevalent in individuals with mental illnesses like schizophrenia, anxiety disorder, post-traumatic-stress disorder, and personality disorders.[6] Observations dating back centuries also note that acute cannabis intoxication can induce specific symptoms of psychosis such as paranoia and hallucinations, as well as general cognitive dysfunction like deficits in attention and memory.[2] Additionally, psychiatric symptoms predict not only problematic cannabis use but also the perception of cannabis as harmless.[6] These reasons, as well as the high prevalence of cannabis use in mentally ill populations, underscore the importance of delineating the potential therapeutic potential of cannabis versus its harms.[6]

Schizophrenia and Psychosis

Schizophrenia is a disease process that is associated with a high risk of long-term disability and decreased quality of life.[9] The average lifetime risk of schizophrenia is estimated to be 0.72%.[9] Like schizophrenia, cannabis use is associated with positive symptoms such as euphoria and

paranoia and negative symptoms such as memory loss.[10] Approximately one in every four individuals with schizophrenia has a concurrent diagnosis of CUD.[6] Given that CUD is grossly underdiagnosed, it is likely that this statistic underestimates the true prevalence of concomitant psychosis and CUD.[6] Studies have shown that regular cannabis users are two times more likely to develop psychosis.[6,11,12] For heavy cannabis users, this likelihood increases to four.[6] It has been shown that schizophrenia and related disorders are more prevalent in patients with CUD compared to those with cocaine use disorder.[13] Cannabis users who develop psychosis are more likely to develop symptoms at a younger age than nonusers.[6] It has also been demonstrated that the administration of intravenous THC to healthy individuals can directly induce both subjective symptoms of psychosis and symptoms qualitatively assessed on the Positive and Negative Symptom Scale (PANSS).[6]

Overall, cannabis use has been shown to be associated with earlier onset of psychosis, increased symptom severity, higher rates of relapse, longer hospitalizations, and poorer outcomes.[6] Young individuals identified as ultra-high risk for psychosis by widely-used criteria who use cannabis have been shown to be 4.90 times more likely to transition to a psychotic disorder than those who deny use.[14] Similarly, in patients with existing schizophrenia diagnoses, continued cannabis use compared to discontinuation and abstinence is associated with more intense positive and negative symptoms, higher rates of relapse, longer hospital admissions, and decreased quality of life.[6] The effects of continued cannabis use have also been studied in individuals without a diagnosis of schizophrenia but with a history of a first episode of psychosis.[10] It is estimated that in North America and Europe, one-third of patients with first-episode psychosis report regular cannabis use, and approximately half of those patients quit following treatment.[15] Those who discontinue cannabis use have fewer positive symptoms and lower frequency of relapse than those who continue.[15] A study of the long-term course of illness in 35 patients in Bangalore found that patients who abstained from cannabis use after their first episode of psychosis underwent full remission and never developed an independent psychotic or mood disorder.[10] Patients who relapsed to cannabis use were more likely to develop independent psychiatric diagnoses.[10] Those who had an earlier onset of cannabis use, younger age at the first episode of psychosis, lower socio-economic status, and family history of psychiatric illness also had worse prognoses.[10] Interestingly, abstinence from cannabis use following relapse did not significantly improve patient outcomes.[10] The association between continued cannabis use and relapse of psychosis was also upheld by a study of 256 patients in southeast London who were treated for the first episode of psychosis between 2002 and 2013.[15] Large and Nielssen found

that the rate of relapse in former cannabis users was 24% compared to 54% in patients who continued low frequency/low potency use and 58% in those who continued high frequency/high potency use.[15] Continued use of high-potency cannabis was strongly correlated with relapse (OR 2.73) even when controlling for non-adherence to medication shown to be associated with cannabis use.[15]

Nestoros and colleagues studied the relationship between cannabinoid metabolite levels in hair, psychotic symptoms, and persistence of symptoms over time.[2] They determined that cannabinoid metabolite levels in hair were not only consistent with patient-reported consumption of cannabis but also were significantly increased in patients with auditory or visual hallucinations, delusions of reference, and delusions of persecution compared to those without these symptoms.[2] These symptoms of psychosis were also found to persist three months after discontinuation of cannabis use.[2]

Given that abstinence from cannabis has been shown to improve memory impairment and other cognitive deficiencies associated with its use, it is unsurprising that cannabis may exacerbate symptoms of psychosis.[6] The exacerbation of specific symptoms of psychosis becomes increasingly important with the growing recognition of psychosis as a dimensional rather than categorical diagnosis.[16] This trend has introduced the concept of schizotypy, which refers to a collection of personality traits related to the risk of psychosis diagnoses such as magical thinking (positive schizotypy), disorganized thought (disorganized schizotypy), and anhedonia (negative schizotypy).[16] A recent study of the relationship between early cannabis use and schizotypy established that early onset of cannabis use (before age 16) was associated with higher levels of introvertive anhedonia only in females.[16] This finding supports not only the study of specific features of psychosis but also the importance of age and sex and moderators.[16]

Despite the association that has been frequently observed between cannabis use and schizophrenia, less has been done to prove a causal relationship.[11] Given the ethical obstacles associated with proving causality in studies of cannabis, alternate approaches to randomized controlled trials have been attempted. One of these approaches uses Mendelian randomization (MR) principles to demonstrate causality between exposure and outcome using genetic markers.[9] This methodology also allows for evaluation of the robustness of causality by testing for the presence of pleiotropy, wherein multiple causal pathways link a single genetic marker to an outcome.[9] Multivariable MR can also adjust causality estimates for confounding risk factors.[9] A recent study by Vaucher and colleagues used ten independent single-nucleotide polymorphisms (SNPs) identified to be associated with ever cannabis use in

a recent genome-wide association study (GWAS) to estimate the causal effect of cannabis use in 34,241 users and 45,604 controls.[9] Using MR, it was shown that ever use of cannabis was significantly associated with increased risk of schizophrenia regardless of tobacco exposure and without pleiotropy.[9] This finding coincides with the evidence that cannabis use affects schizophrenia-affected cerebral cannabinoid receptors, cortical maturation, and addiction mechanisms.[9]

To put the MR data into perspective, it is clear that most individuals who use cannabis never develop a psychotic disorder.[11] It is thought that cannabis use and the development of psychosis are linked by an underlying genetic vulnerability.[11] It is unclear whether a potential genetic vulnerability predisposes individuals to both using cannabis and developing psychosis or if vulnerable individuals can avoid progression to psychosis by avoiding the drug.[11] Aas and colleagues used GWAS data to assign a polygenic risk score (PGRS) to patients with a schizophrenia spectrum disorder and to healthy controls to determine whether there was a relationship between schizophrenia risk and cannabis use.[11] Higher PGRS was associated with greater genetic risk for developing a schizophrenia spectrum disorder.[11] When schizophrenic patients were split into two groups (frequent, daily or weekly, users and infrequent or never users), an association was seen between frequent cannabis use before illness onset and high PGRS.[11] Frequent users of cannabis who started using prior to age 18 had the highest PGRS of any group.[11] This data supports an overlapping genetic susceptibility to cannabis use and development of schizophrenia but requires further investigation given the reliance on GWAS accuracy and lack of cannabis use data for controls.[11]

The need for continued research of gene-environment interaction in relation to cannabis use is underscored by a recent study of the interaction between catechol-O-methyl transferase (COMT) polymorphism Val158Met with cannabis exposure.[17] This polymorphism is thought to have a moderating effect on the relationship between cannabis use and the emergence of the psychosis phenotype.[17] In their transdiagnostic meta-analysis, Vaessen and colleagues determined a significant interaction between cannabis use and the COMT polymorphism, but this interaction was only significant in case-only studies.[17] Given that studies with a case-only design have lower validity than studies using dichotomous or continuous outcomes, more convincing evidence of the interaction is required moving forward.[17]

Of importance in this discussion is the aforementioned distinction between THC and CBD. The use of the combination of THC and CBD found in cannabis and THC alone seems to be associated with negative outcomes in schizophrenia.[9] It appears that the use of CBD

alone, however, may have opposite effects.[9] CBD has been shown to have similar efficacy of symptom improvement to popular antipsychotics like amisulpride.[9] Daily intake of 1000 mg of CBD as an adjunct to antipsychotic therapy has been shown to decrease positive symptoms on the PANSS.[6]

Anxiety

Research regarding the relationship of cannabis to psychiatric disorders has been unevenly distributed among different diagnoses.[18] A significant research effort has resulted in robust evidence for the association between cannabis use and psychosis, as described above. There is less literature on cannabis and anxiety despite hypotheses that THC may elicit anxiety symptoms through its effects on serotonin and norepinephrine.[17] Of the existing evidence, very little data stems from studies available for longitudinal analysis.[17] The data also do not reflect the potential for reverse causality, in which anxiety serves as the predisposing factor for cannabis use due to the short-term relaxation effects associated with the drug.[17]

A recent meta-analysis of ten studies aimed to address a few of the shortcomings of previous work on cannabis and anxiety, including limited sample size, reverse causality, and limited generalizability.[17] This random-effects meta-analysis used a combined sample size of 58,538 individuals, most of whom were adolescents and young adults, from studies systematically selected through May 2016.[17] Cannabis exposure and anxiety were coded as binary variables.[17] Anxiety was diagnosed via the Diagnostic and Statistical Manual of Mental Disorders (DSM).[17] Studies investigating specific subsets of anxiety disorders were excluded, and baseline anxiety was assumed to be relatively low since samples were selected from the general population.[17] The main analysis supported an association of cannabis use with anxiety with a small OR of 1.15.[17] This OR decreased to 1.04 when the analysis was limited to high-quality studies, suggesting that cannabis use is, at most, a minor risk factor for the development of anxiety symptoms in the general population.[17] These data are complemented by a developmental molecular-genetic study of adolescent cannabis users that focused on a polymorphism involving a serotonin transporter gene.[18] In considering the effects of cannabis on symptoms of anxiety in 1424 adolescents over the course of five years, it was determined that cannabis use is associated with an increase in anxiety symptoms only in carriers of the short allele of the 5-HTTLPR gene.[18]

Prospective studies of cannabis use and mental health have also aimed to consider associations on a broader scale in the general adult

population.[19] A nationally representative sample of 34,653 US adults, aged 18 or older, in the National Epidemiologic Survey on Alcohol and Related Conditions in two waves: 2001–2002 and three years later, 2004–2005.[19] Multiple regression analysis and propensity score matching were used to evaluate associations between cannabis use at wave one and DSM diagnosis of psychiatric disorder at wave two.[19] It was determined that cannabis use at wave one was significantly associated with any substance disorder (OR 6.2), any alcohol use disorder (OR 2.7), any cannabis use disorder (9.5), any other drug use disorder (OR 2.6), and nicotine dependence (OR 1.7).[19] Cannabis use was not associated with any mood disorder (OR 1.1) or anxiety disorder (OR 0.9).[19]These findings, while furthering the notion that there is no real association between cannabis use and anxiety, are not to be overlooked considering substance abuse disorders cost the US an estimated $700 billion annually.[19] The current literature suggests that cannabis use alone is not sufficient for the development of long-term anxiety and is at most a minor risk factor that may operate in conjunction with other factors. The evidence for an association between anxiety and cannabis is mixed likely due at least in part to the opposing biological effects of THC and CBD.

Depression

It is known that cannabis use is more prevalent among patients with major depressive disorder (MDD) compared to the general population. Depression is a significant burden on modern healthcare.[21,22] Depression has been associated with significant comorbidities.[23] Still the evidence regarding the effects of cannabis on depression symptoms is varied.[5] Some studies have reported that cannabis can be therapeutic for individuals with depression, while others have shown that the drug can exacerbate symptoms.[5] It is thought that for some, cannabis acts as an outlet for their depressive symptoms, while for others, cannabis causes a heightening of dulled emotions and anhedonia.[5] The brain reward system may link the actions of cannabis to the pathogenesis of MDD.[5] This conflicting evidence is concerning given that cannabis may be a contributor to not only to MDD but also to suicidal behaviors, especially in young people.[5]

One of the more popular theories regarding the interaction of cannabis and MDD involves a focus on metabolic and oxidative stress.[5] There is a growing body of literature that supports an oxidative stress hypothesis of depressive disorder, which governs that depression is characterized by a state of decreased antioxidant status with lowered concentrations of known antioxidants like tryptophan, vitamin E, tyrosine,

and glutathione.[5,24] Khadrawy and colleagues recently investigated the effects of cannabis on baseline levels of oxidative stress in a rat model of depression.[5] Depression was brought on in rats using the well-studied method of reserpine induction, which not only causes anhedonia, low feeding, and reduced locomotion in rats but also depletes serotonin levels.[5] When depressive-like rats were treated with *Cannabis sativa* extract (10 mg/kg of THC), they were observed to experience decreased motor activity, decreased monoamine levels, and significantly increased acetylcholinesterase activity in the hippocampus and cortex.[5] Increased levels of nitric oxide and lipid peroxidation in these two brain regions were indicative of an oxidative state.[5] Considering the fact that there was no evidence of improvement in behavior or neurochemical makeup in the depressive-like rats, the results of the study support the hypothesis that individuals with depression experience exacerbation of their symptoms with cannabis use.[5]

As the aforementioned trend toward increased access to higher-potency cannabis continues, it becomes important to consider how the effects of this substance differ with varying potency.[8] The market for cannabis in the United Kingdom has been inundated by high-potency varieties of cannabis such as skunk, sensimilla, hash, and resin, whose THC content can reach up to 15%.[8] In the US, a trend toward higher potency cannabis has been driven by the medicinal cannabis industry, which is striving to allow patients to use smaller doses of higher potency cannabis to limit their exposure to smoked herbal products.[8] Butane hash oil (BHO), also referred to as "dabs" or "shatter" is an extracted form of cannabis concentrate that can contain a THC content as high as 76%.[8] Given the thinking that higher potency cannabis can be associated with greater harms, a study using a very large sample of drug users in the Global Drug Survey (GDS) from 2015 and 2016 evaluated cannabis use and lifetime diagnoses of depression, anxiety, and psychosis.[8] It was determined that individuals with a lifetime diagnosis of depression, anxiety, and substance abuse were more likely to use extremely high potency forms of cannabis such as BHO than high potency herbal cannabis.[8] These users also reported more subjective negative effects and fewer positive experiences associated with BHO use compared to herbal cannabis use. Interestingly, the use of BHO was more common in individuals using cannabis for medicinal purposes.[8] This propensity for the use of BHO and higher potency cannabis in individuals with depression and those using it for medicinal purposes is alarming given the fact that CUD may be associated with decreased quality of life, reduced efficacy of pharmacological treatments, and poorer everyday function in individuals with MDD.[8,20]

Personality Disorder

Links between specific types of personality disorders (PD) and substance abuse, including cannabis, have been established in the literature.[21] For a long time, studies focused on specific PD diagnoses but failed to examine how the association with cannabis could vary among PD as a whole.[21] A twin study of 1,419 total subjects, with standing DSM-IV diagnoses, established that antisocial and borderline PDs were strongly associated with cannabis use and CUD.[21] In this study, lifetime cannabis use and CUD were evaluated using DSM-IV criteria for cannabis abuse and dependence.[21] Dependence, withdrawal, and craving were also assessed.[21] This finding indicated that antisocial and borderline PD have the strongest genetic and phenotypic correlates to cannabis use and misuse.[21] Antisocial and borderline PDs have also previously been shown to be strongly associated with alcohol use and misuse based on genotypic and phenotypic liability.[21] This similarity is unsurprising considering the comorbidity associated with substance use and abuse, but this study supports that the same genetic risks may account for borderline PD, antisocial PD, and cannabis/alcohol use and abuse.[21] What is more surprising about the results of this study is that schizotypal and narcissistic PDs were not found to be related to cannabis use or abuse.[21]

Conclusion

Cannabis use has increased over the recent years due to the shifting of societal and legal perceptions, and thus it has become imperative to better understand the basic science and clinical applications of this compound. However, cannabis use disorder (CUD) is highly prevalent in individuals with mental illness, and thus it is critical to delineate potential therapeutic benefits of cannabis from its risks and impact on mental illnesses.

It has been shown that cannabis use is correlated with both increased likelihood and earlier onset of psychosis, as well as more intense schizophrenic symptoms in patients with existing schizophrenia diagnoses. Though is suspected that the development of psychosis and cannabis use may be linked by an underlying genetic component (such as the COMT Val158Met polymorphism), this hypothesis requires further investigation and evidence at this time.

The effects of cannabis use on other conditions, such as major depressive disorder (MDD) must also be further quantified. Though the effects of cannabis use on depression symptoms is unclear, it has been shown that individuals who use cannabis for medicinal purposes are more inclined to use higher potency varieties of cannabis such as BHO.

These forms of cannabis have also been associated with more subjective negative effects and fewer positive experiences when compared to herbal cannabis use.

Given the fact that at present, distribution of medicinal cannabis is better regulated than that of recreational cannabis, it may be possible to conduct structured studies of cannabis dosage in patients using medical cannabis. ✤

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