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Cannabis and development of dual diagnoses: a literature review

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Abstract

Background—The use of cannabis has garnered more attention recently with ongoing efforts at marijuana legalization. The consequences of cannabis use are not clearly understood and remain a concern.

Objectives—to review the acute and persistent effects of cannabis use and associations with psychiatric disorders

Methods—Using Pubmed and PsychInfo, we conducted a narrative review of the literature on cannabis and psychiatric comorbidity using the keywords cannab*, marijuana, schizo*, psychosis, mood, depression, mania, bipolar and anxiety.

Results—There is substantial evidence of cannabis use leading to other illicit drug use and of an association between cannabis use and psychosis. A few reports suggest an association with bipolar disorder while the association with depression and anxiety disorders is mixed.

Conclusions—Whenever an association is observed between cannabis use and psychiatric disorders, the relationship is generally an adverse one. Age at the time of cannabis use appears to be an important factor with stronger associations observed between adolescent onset cannabis use and later onset of psychiatric disorders. Additional studies taking into account potential confounds (such as withdrawal symptoms, periods of abstinence and other substance use) and moderators (such as age of initiation of cannabis use, amount and frequency of drug use, prior history of childhood maltreatment and gender) are needed to better understand the psychiatric consequences of cannabis use.

Keywords

marijuana; psychosis; schizophrenia; depression; anxiety; bipolar; mania; cognition; adolescence

Introduction

An estimated 22.2 million Americans were current users of cannabis in 2014.

Approximately 6.8 million were in the 18–25 age group and another 1.8 million were between 12 and 18 years of age[1]. Cannabis is increasingly viewed as a ‘soft drug’ with about 70% of high school seniors believing regular use is not very harmful, compared to about 20% who held this view in 1990[2]. This is of particular concern as the adolescent

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brain is believed to be particularly susceptible to adverse effects of cannabis. Cannabis use has been associated with psychiatric comorbidity including mood and anxiety disorders and psychosis[3], particularly with early initiation of cannabis use[4]. This relationship between cannabis use and psychiatric comorbidity is not, however, clearly understood, with inconsistent and even contradictory findings. In this review, we examine the acute effects of cannabis followed by a review of the persistent effects of cannabis in relation to psychiatric disorders.

Methods

Using Pubmed and PsychInfo, we conducted a narrative review of the literature on cannabis and psychiatric comorbidity using the keywords cannab*, marijuana, schizo*, psychosis, mood, depression, mania, bipolar and anxiety. The search was conducted on December 12, 2015. Of approximately 8000 hits, 198 cannabis-related studies conducted in humans, that utilized psychiatric assessment scales, were included.

1. Acute effects of cannabis use

a) Healthy individuals—Cannabis intoxication includes feelings of relaxation, euphoria or feeling “high”, increased sociability, decreased anxiety and boredom, and enhanced sensory-perceptive experiences[5–10]. In particular, non-clinical populations consistently rank relaxation high as a reason for use. Cannabis intoxication can, however, lead to undesirable experiences, such as increased anxiety or panic, cognitive impairment, and psychotomimetic effects including paranoia, grandiosity, depersonalization, derealization, disorganized thinking, hallucinations, and other perceptual distortions[5, 6, 10–14]. Dose-dependent psychotic experiences have been reported by 15–50% of individuals in community surveys[6, 7, 12, 13]with symptoms resolving within a few hours[5]. These anecdotal observations have been explored in different experimental paradigms. Naturalistic studies that examine the effects when individuals use their own cannabis in their accustomed manner and environment have the advantage of capturing real life use[15–17]. These studies consistently report an increase in psychotic-like experiences[15–17], as well as improvements in positive affect[16] and perception of the friendliness of others[15].

Laboratory-based studies have the advantage of controlling for the type and amount of the substance consumed. Early studies typically used smoked or oral cannabis with attempts to quantify administered ⁹tetrahydrocannabinol (THC). These studies reported THC-induced core symptoms of psychosis at higher doses, including thought disorder, paranoia, perceptual distortions and hallucinations[18–22], as well as detachment from reality, euphoria and uncontrollable mirth, and impaired time perception[18, 19]. More recent stringent studies controlling for amount of THC in intravenous[23–27] or oral[28–30] preparations and use of standardized scales demonstrate transient increases in positive symptoms of psychosis[23, 24, 26–28], including paranoia, grandiosity, sensory distortions and hallucinations, depersonalization, derealization and thought disorganization. Negative symptoms of psychosis, including decreased affective range, spontaneity, and rapport, as well as psychomotor retardation and emotional withdrawal, were also reported in several studies[23, 25, 26] and determined not to be related to self-rated sedation[25], though other

confounders cannot be excluded[23]. Transient impairments in cognition were consistently demonstrated[23, 24, 26, 27, 29], most notably immediate and delayed recall[23, 24, 29] and often[23, 24, 26, 27], but not always[29], working memory. Binocular depth inversion, a measure of visual information processing that is impaired in psychotic states, was noted to be impaired in healthy subjects given oral THC, similar to prodromal and schizophrenia comparison groups[30]. Volunteers were observed to appear transiently dysphoric but would report feeling more relaxed[24], physical and mental sedation[24, 28], and subjective feeling of intoxication or being “stoned”[28, 29]. Effects were reported to peak within 10–30 minutes and resolve within 120 min after IV THC[23, 24] and peak around 2 hours and then began to resolve after oral THC[28, 29], with the exception of feeling intoxicated which was somewhat more persistent[29]. Studies of medicinal cannabinoids used to treat pain, nausea, and spasms related to neurological disease, including dronabinol (synthetic THC), levonantradol, and nabilone, have shown similar effects (reviewed in[13]). Frequency of cannabis use has been shown to impact the acute effects of THC, with more frequent users demonstrating less marked psychotic-like symptoms, anxiety, cognitive impairment, and time distortion[31–33] though euphoric effects were similar[31]. Higher doses of THC result in greater psychotic symptoms in both anecdotal descriptions[34] and experimental studies[19, 22, 23, 35] as well as greater cognitive impairment[23, 29]. Biphase anxiety responses are noted for cannabinoids with lower doses associated with anxiolytic and higher doses with anxiogenic effects[36].

Cannabidiol (CBD) is another cannabinoid in cannabis that has been shown to attenuate some of the adverse effects of THC. Several studies report more severe positive psychotic symptoms when the THC/CBD ratio is high[37, 38], though this is not universal[39]. Controlled studies administering THC with or without CBD demonstrate that CBD attenuates the psychotomimetic, anxiogenic, and cognition-impairing effects of THC[37, 40–45], particularly when administered simultaneously. Cannabinoids bind to cannabinoid receptors that are highly expressed in the brain. Synthetic cannabinoids are more potent full agonists at the cannabinoid 1 receptor (CB1R), as compared to the partial agonist effects of THC. Case reports or case series of synthetic cannabinoids, often called K2 or Spice, report florid psychosis resolving with intoxication and more persistent psychosis lasting weeks or months even in individuals without a psychiatric history [termed ‘spicephrenia’ (reviewed in[46])], as well relapse in those with psychotic disorders,

b) Individuals with psychosis—When describing reasons for cannabis use, individuals with psychosis rank relief of dysphoria, which includes relaxation (66.3%), followed by social reasons (61.7%) and enhancement of positive affect (42.1%)[47]. Illness and medication-related reasons were less commonly reported (12.9%). In reporting effects of cannabis use, positive effects on affect and relaxation were common, whereas negative effects on symptoms and side effects were mentioned by up to 45% of patients. Amelioration of psychotic symptoms was reported about 10% of the time[8]·[9].

The acute use of cannabis in patients with schizophrenia can lead to re-emergence or worsening of symptoms and even require hospitalization in those who were psychiatrically stable and adherent to medications[48]. A naturalistic study of individuals using their own cannabis and reporting on their experiences at prompted intervals compared individuals with

psychosis to healthy controls[16]. Both psychosis and control groups experienced improvement in positive affect and increase in hallucinations after smoking cannabis. However, cannabis had a much greater effect on worsening negative affect and increasing hallucinations in the psychosis group compared to the control group. The timing, with greater improvements in positive affect immediately after cannabis use and delayed increases in hallucinations may explain cannabis use despite worsening positive symptoms in this population.

An early study administering hashish to individuals with psychotic disorders noted exacerbation of symptoms[49]. D'souza et al.[35] administered intravenous THC to individuals with schizophrenia who were clinically stable and on their current antipsychotic regimen. Compared to healthy controls without personal or family psychiatric history[23], the psychosis group demonstrated greater sensitivity to the psychotomimetic and cognitive effects of THC. Negative symptom exacerbation was mild on standardized measures but appreciable on exam. Interestingly, no beneficial effects, such as euphoria, were found. In contrast, Henquet et al.[50], who provided controlled amounts of THC to a combined population of psychosis, relatives of psychosis, and controls without personal or family history of mental illness, did not demonstrate an effect of THC on psychosis-like symptoms, though it did impair memory and sustained attention measures.

2. Persistent effects of cannabis

Several studies suggest an association between cannabis use and psychiatric disorders including depression, mania, anxiety and psychosis. Other studies, however, do not support these findings or find that confounding factors can explain the associations. The potential detrimental consequences of cannabis use remain controversial. Cannabis use during adolescence, while the brain is still developing, might lead to very different sequelae compared to drug use in adulthood. In this section, we examine the relationships between cannabis use and psychiatric illnesses with an emphasis on the age of onset of cannabis use and later manifestation of psychiatric disorders.

a). Addiction—The lifetime risk of cannabis users developing cannabis dependence is estimated to be around 9%. This risk increased to approximately 16% if cannabis use was initiated during adolescence[51] and to 25–50% among those who used cannabis on a daily basis[52]. Whether cannabis serves as a gateway drug (i.e. cannabis use increases use of other illicit drugs) is debated. Associations between cannabis use and use of other illicit [53–56] and novel psychoactive substances [57–59] including temporal relationships between cannabis use and other illicit drug use[54, 60–62] have been reported. A 25 year longitudinal study that conducted annual assessments of illicit drug use found that regular or heavy cannabis use was associated with an increased risk of using other illicit drugs[60], observations similar to other studies[63, 64]. This association was found to be particularly strong with adolescent cannabis use. In an integrated analysis of three longitudinal studies[65], daily cannabis users before age 17 had significantly increased odds of later cannabis dependence and other illicit drug use.

b). Psychosis—Cannabis has also been associated with episodes of psychosis persisting beyond the period of intoxication, with case series reported from different countries[13, 34, 66–71]. The psychotic episode itself is described in different ways, including reports describing disorientation, confusion, and amnesia as part of this syndrome[72], which some separately classify as a “toxic psychosis”[10, 34, 73]. Typically, cannabis-induced psychotic episodes are precipitated after the use of large amounts of cannabis, resolve with abstinence, and are of shorter duration than those observed with primary psychotic disorders[13]. However, large-scale studies in Denmark and Finland demonstrate that nearly 50% of those initially diagnosed with cannabis-induced psychosis will ultimately be determined to have a schizophrenia spectrum disorder[74, 75].

Cannabis use disorders are common in schizophrenia with a recent meta-analysis estimating current cannabis use at 16% and life-time cannabis use at 27% with higher rates in males and in first episode subjects[76]. Cross-sectional and longitudinal studies show a consistent relationship between cannabis use and psychotic disorders (previously reviewed[13, 77, 78]). Several studies show that cannabis use occurs prior to onset of psychosis [79–81] and is associated with earlier onset of illness[82–86]. There is evidence, however, that other factors influence this earlier onset[87], including age of cannabis use[88], gender[88, 89] and genetic risk factors[90]. A recent meta-analysis concluded that cannabis use is associated with earlier onset of approximately 3 years with the interval between age of onset of cannabis use and onset of psychosis to be about 6 years[91]. Further, onset of cannabis use at younger ages[92] and the frequent use of more potent strains of cannabis are associated with higher risk of developing psychosis[93]. The temporal relationship and dose response relationship between cannabis use and developing psychosis[94, 95] provides indirect evidence of causality although there is also some evidence for a bidirectional association[96, 97]. Childhood maltreatment is associated with increased adolescent cannabis use[98] and also moderates the association between cannabis use and psychosis[99, 100] with evidence of a dose-dependent effect [101].

An unexpected and interesting observation linking prior cannabis use in schizophrenia to better cognitive function, compared to individuals with schizophrenia without a cannabis use history, has been reported in many[84, 102–116], but not all studies[117–119]. This is opposite to the pattern observed in cannabis users who are otherwise healthy[120]. Two meta-analyses support the observation that previous cannabis use in schizophrenia is associated with less cognitive impairment[105, 121]. One meta-analysis of eight studies comparing schizophrenia with and without a history of cannabis use excluded concurrent substance use disorders and found differences of moderate effect size for general cognition and small effect size for attention and visuospatial abilities, all suggesting better cognitive functioning in prior cannabis users compared to non-users.

Findings from studies that examined adolescent onset of cannabis use and cognitive performance in individuals with psychotic illnesses are more consistent. All of these studies show that adolescent cannabis use is associated with improved cognitive function[103, 107, 116, 122–124], contrary to the observation in otherwise healthy controls[125–127]. Two studies with abstinent periods more than one month [103, 108] found that earlier onset cannabis use in schizophrenia was associated with better cognitive function in those with

psychosis while the reverse pattern was seen in otherwise healthy controls. Cannabis use is generally associated with deleterious outcomes and this paradoxical association of age-dependent cannabis use and less impaired cognitive function in schizophrenia needs further investigation.

c). Depression—There are reports of cannabis use increasing the odds of depression [128, 129] but results from longitudinal studies are mixed with some reporting associations while others did not find relationships independent of other psychosocial factors or confounds. Previous reviews[130–132] have described modest associations between cannabis use and depression with suggestion of associations between early-onset, regular cannabis use and later depression. A recent meta-analysis of longitudinal studies reports an increased risk of depression in cannabis users [131] with one study finding evidence of bi-directionality [133]. A more recent study using multiple models of analysis accounting for various covariates did not find differences between cannabis users and non-users[134], and, on the contrary, found evidence of a reverse relationship i.e. MDD (major depressive disorder) was associated with increased incidence of cannabis use.

When associations between adolescent cannabis use and later depression have been examined, significant associations have been reported in several [79, 135–142] but not all[4, 143–146] studies. A population-based study using data from 17 countries reported an increased risk ratio of 1.5 for depression with onset of cannabis use before age 17[147]. On the other hand, two longitudinal studies spanning adolescence to adulthood did not find any association between cannabis use and depression[4, 148], although one did observe a dose-dependent relationship between cannabis use and suicidal ideation and attempts. Similar observation of a relationship between cannabis and suicidality, but not MDD, has been observed in other studies, particularly if cannabis use onset occurred during adolescence [65] [149]. There could be a gender effect with some studies reporting an increased risk of depression in female cannabis users[55, 139, 150] although the reverse has also been reported[151].

d). Bipolar disorder—Cannabis is the most frequently used illicit substance in bipolar disorder[152–155]. Associations between cannabis use and bipolar disorder have been reported[142, 156–158] but not examined to the same depth as in psychotic illnesses or depression (recent reviews[134, 155, 159]). There is evidence that premorbid cannabis use predicts development of bipolar disorder[160–163] and an earlier age of onset[154, 164–166] and even some evidence of a dose response relationship[167]. On the other hand, there are also reports of cannabis use beginning after the emergence of bipolar disorder[168, 169], especially in children and adolescents[170], with reports of affected individuals using the drug to alleviate symptoms[171, 172]. A recent study, however, did not support the idea that cannabis is used by individuals with bipolar disorder to treat their symptoms[173]. On the contrary, this study suggests that positive affect increased the odds of using cannabis. A prospective study in high risk adolescents examined the temporal course of associations between substance use (35 of the 50 subjects met cannabis use disorder criteria) and bipolar disorder found a pattern of increased substance abuse in emerging bipolar disorder[174]. Childhood abuse may moderate this association with evidence for additive effects between

cannabis abuse and maltreatment on age of onset of bipolar illness[175]. Lastly, two studies examining the association between cannabis use and cognitive function in bipolar disorder[119, 176] report better cognitive performance in some domains in cannabis users. Of note, the cannabis users were more likely to experience psychosis during acute episodes[176].

e). Anxiety—There is increased comorbidity between cannabis use and anxiety disorders[143, 177–179] including generalized anxiety disorder, panic disorder, social anxiety, obsessive compulsive disorder and post-traumatic stress disorder[4, 142, 180–185] (recent reviews[14, 186]) with prevalence of an anxiety disorder in chronic cannabis users estimated to be approximately 20%[6]. Some cross sectional and prospective studies find increased associations between cannabis use and anxiety disorders[4, 140] but others do not, particularly after controlling for potential confounds[142, 179]. A recent meta-analysis of 31 studies [186] reported a small positive association between anxiety and cannabis use and cannabis use disorders. There is some suggestion that anxiety disorders predict later cannabis use[178] and that females may have an increased vulnerability[139]. Conversely, one prospective 15 year study reported that adolescent cannabis use [89, 187] was associated with an increase in anxiety at age 29 even if they had ceased using cannabis. This association was higher in those with a history of daily adolescent cannabis use[4].

Discussion

While the desired effects of acute cannabis intoxication include relaxation, euphoria and decreased anxiety, there are some individuals who experience aversive effects such as an increase in anxiety, paranoia and hallucinations. This is related to the type and strain of cannabis (e.g. THC concentration or THC/CBD ratio), amount of cannabis used and/or could reflect biologic differences between individuals. A large body of literature related to associations between cannabis use and psychiatric illnesses have produced mixed findings. In general, however, whenever there is an association between cannabis use and later psychiatric sequelae, the outcome is a deleterious one. This is particularly true when cannabis use is initiated at younger ages and with heavier cannabis use. There is evidence that cannabis may serve as a gateway drug to other illicit drug use and also with later onset of psychosis. The data are mixed and inconclusive with regards to the temporal associations between cannabis use and depression and anxiety disorders. Studies examining cannabis use and bipolar disorder are relatively scarce compared to other psychiatric disorders and while some studies have suggested a causal relationship, the available data are mixed. There is one surprising observation that relates to cognitive function in individuals diagnosed with schizophrenia or schizoaffective (SCZ) disorder. Individuals with SCZ with a history of cannabis use during adolescence exhibit better cognitive function when compared to those with SCZ without a cannabis use history. It has been suggested that SCZ associated with adolescent cannabis use may represent a schizophrenia subgroup.

There are several factors that might be contributing to the mixed results reported in the literature. First, the definition of cannabis use and the characterization of cannabis use varies between studies. Many studies rely on self-report of cannabis use that might be prone to bias. In addition, the age of onset of cannabis use, frequency and duration of use are all

important factors in determining long term effects of cannabis. The potency of cannabis used and relative concentrations of THC and CBD are important factors to consider as well. Secondly, outcome measures differ widely among studies. The timing of assessments is critical given that cessation of cannabis use can lead to withdrawal symptoms and possibly residual effects that might impact outcome measures. Assessments themselves have varied with some studies measuring symptoms (e.g. symptom of depressed mood) while others have focused on clear diagnostic criteria of psychiatric illnesses (e.g. MDD). Baseline measures of illness severity is another potential confound to consider. Third, many studies do not control for important confounding factors such as alcohol and other substance use and basic socio-demographic characteristics and psychosocial factors such as family disadvantage. There is some evidence of gender differences in cannabis use and later substance use, anxiety and depression. Childhood trauma has also shown to be associated with cannabis use and with psychiatric illnesses, particularly psychosis and bipolar disorder, the interaction of which will need to be better understood. It will be important to address these variables and potential confounds in future studies.

There is substantial evidence suggesting that cannabis use during adolescence increases the risk of developing schizophrenia and some evidence, although inconsistent, for an increased risk of mood and anxiety disorders. This raises the possibility that the adolescent brain might be 'sensitive' to the effects of cannabinoids. This implies that the adolescent brain might be different from the adult brain in terms of its response to cannabis. There is evidence of this from rodent studies that find adolescent cannabinoid 1 (CB1) receptors are less functionally active, desensitize and develop tolerance to THC more slowly when compared to adult CB1 receptors. This may be one reason that adolescent rodents find THC less aversive[188], raising the possibility that adolescent drug use is associated with greater reward and setting the stage for continued drug use[188]. THC or synthetic cannabinoid administration during adolescence lead to long term learning and memory [188–191] and behavioral deficits[189, 190, 192–194] in rodents, including increased drug use later in life[195, 196]. At the molecular level, there is evidence of adolescent cannabinoid exposure leading to persistent changes in CB1R and genes involved in endocannabinoid signaling[192, 195, 197–199]. There may be gender differences in CB1R expression with higher levels reported in males[194, 197, 200]. There are also studies reporting that chronic adolescent cannabinoid exposure leads to changes in the GABA and glutamate systems, neuronal morphology and white matter gene expression. For example, adolescent cannabinoid exposure inhibits the developmental switch in NMDA (N-methyl-D-aspartate) receptor subunit composition from mainly GluN2B-containing NMDA receptors to mainly GluN2A-containing receptors in female rats[192], modulates GABA (γ -Aminobutyric acid)-related gene expression and neurotransmission[201, 202] and leads to changes in neuronal morphology, with reduced spine density in the prefrontal cortex and hippocampus[192, 193], reduced neurogenesis[203] and changes in white matter genes such as myelin basic protein [204, 205]. Taken together, these rodent studies suggest that the adolescent brain is susceptible to exogenous cannabinoids and that exposure to cannabinoids during this vulnerable period has lasting effects on excitatory and inhibitory circuits, pyramidal dendritic morphology and myelination that are associated with long term behavioral sequelae.

Some, but not all, individuals using cannabis have an increased risk of later drug use or psychiatric disorders. This may reflect a genetic vulnerability, The risk of cannabis abuse runs in families[206]. Several studies have examined the candidate genes, cannabinoid receptor 1 (CNR1) and fatty acid amide hydrolase (FAAH; enzyme involved in endocannabinoid metabolism), and drug dependence. CNR1 single nucleotide polymorphisms rs806368 and rs6454674 and FAAH rs324420 (C385A) have been associated with drug addiction[207]. A meta-analysis of 11 studies of three CNR1 polymorphisms found that only long repeats of the AAT triplet repeat polymorphism in Caucasians was associated with substance use disorders[208]. There are functional and brain structural findings associated with certain polymorphisms. For example, the CNR1 rs2023239 G allele is associated with increased cannabis cue reactivity in reward-related areas of the brain, such as the orbitofrontal cortex, inferior frontal gyrus and anterior cingulate[209] and reduced hippocampal volumes[210] while the C allele is associated with trait anxiety[211] and negative affect in abstinence[212]. The vast majority of studies linking candidate genes and cannabis use to psychiatric symptoms are related to schizophrenia or psychotic illnesses. Several studies support a relationship between family psychiatric history and increased likelihood of psychotic symptoms associated with cannabis use [213–215]. Psychosis liability has also been shown to potentiate the psychotomimetic effects of acute cannabis use[15, 17]. Several candidate genes include COMT (catechol-o-methyl transferase), dopamine receptor 2 (DRD2), AKT1, BDNF (brain derived neurotrophic factor) and neuregulin1 (NRG1) are reported to interact with cannabis use. The gene that has attracted the most interest is COMT. An initial study of the common functional single nucleotide polymorphism (SNP) Val158Met showed that adolescent cannabis use in Val homozygotes had a much higher risk of developing psychosis in adulthood. These findings were supported by some[50, 216] but not all studies[217]. More recently, a 3 way interaction between cannabis use, childhood abuse and COMT genotype has been reported[218]. This SNP is an interesting candidate gene with biologic plausibility given that the high activity COMT val isoform is associated with lower synaptic dopamine levels which is relevant to schizophrenia pathophysiology. Recently, a functional SNP, rs1076560, in dopamine receptor 2 (DRD2) was found to interact with cannabis use to increase the probability of having a psychotic disorder[219]. DRD2 is the target of antipsychotic medications and is also implicated in striatal activity. An association between AKT1, cannabis and psychosis has been shown in two studies. Cannabis use in C/C homozygotes of AKT1 rs2494732 was associated with an increased risk of developing psychosis[220] with heavier users showing more risk[221]. Decoster et al. showed that cannabis-using female psychosis patients carrying the Met allele of the Val66Met BDNF polymorphism developed psychosis 7 years earlier than non-using counterparts with the Val allele[222]. NRG1, a gene involved in neurodevelopmental processes such as myelination, axon guidance, neuronal migration, and glial differentiation[223, 224] interacts with cannabis. Acute THC administration to NRG1 C/C homozygotes at rs7834206 exhibit altered auditory information processing, a schizophrenia phenotype [225]. Several of these candidate genes (e.g., *COMT*, *DRD2*, *AKT1*, and *BDNF*) can impact similar functional pathways (e.g. dopamine signaling), raising the possibility of shared genetic vulnerability for cannabis use and psychosis, i.e. the same genes that increase psychosis risk also raise risk of cannabis use. While there is evidence suggesting causality in the cannabis-psychosis association (e.g. temporal

relationship and dose response), there is also evidence of shared genetic over-lap with a recent study reporting that healthy individuals with a polygenic risk profile of genetic predisposition to schizophrenia were more likely to use cannabis[226].

In summary, the evidence for an association between cannabis use and psychosis is strong but causality has not been clearly established. The evidence of an association with mood and anxiety disorders is weaker and inconclusive. The initiation of cannabis during adolescence appears to be associated with an increased risk of developing psychiatric disorders later in life, particularly psychotic disorders, which may be mediated through interactions with genetic risk factors. It is critical that we further this line of research by collecting converging evidence from temporally detailed epidemiologic studies along with genetic and neurobiologic approaches to better understand whether cannabis plays a role in the later development of one or more psychiatric disorders.

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