

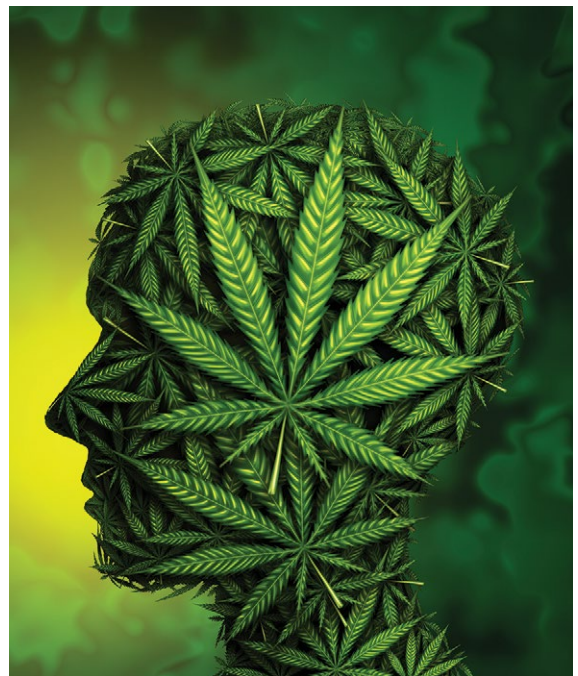
Cannabis and schizophrenia: A complex relationship

For some who are predisposed to psychosis, cannabis may trigger or exacerbate symptoms

Approximately 1 in 200 individuals will be diagnosed with schizophrenia in their lifetime.¹ DSM-5 criteria for the diagnosis of schizophrenia require the presence of ≥ 2 of 5 symptoms: delusions, hallucinations, disordered speech, grossly disorganized (or catatonic) behavior, and negative symptoms such as flat affect or avolition.² Multiple studies have found increased rates of cannabis use among patients with schizophrenia. Because cognitive deficits are the chief predictor of clinical outcomes and quality of life in individuals with schizophrenia, the cognitive effects of cannabis use among these patients are of clinical significance.³ As legislation increasingly allows for the sale, possession, and consumption of cannabis, it is crucial to provide clinicians with evidence-based recommendations for treating patients who regularly use cannabis (approximately 8% of the adult population³). In this article, we analyze several peer-reviewed studies to investigate the impact of cannabis use on the onset and development of schizophrenia.

A look at substance-induced psychosis

Schizophrenia is associated with several structural brain changes, and some of these changes may be influenced by cannabis use (*Box, page 44*). The biochemical etiology of schizophrenia is poorly understood but thought to involve dopamine, glutamate, serotonin, and gamma-aminobutyric



WILDPXL/ISTOCK/GETTY IMAGES

Joseph M. Maes, BS

Medical Student
Creighton University School of Medicine
Omaha, Nebraska

Charlotte A. Ritchie, MD

PGY-1 Psychiatry Resident
Department of Psychiatry
University of Nebraska Medical Center
Omaha, Nebraska

Sriram Ramaswamy, MD

Professor of Psychiatry
Department of Psychiatry
Creighton University School of Medicine
Omaha, Nebraska

Disclosures

Dr. Ramaswamy receives research support from Bristol Myers Squibb and Forest Pharmaceuticals. Joseph M. Maes and Dr. Ritchie report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

doi: 10.12788/cp.0417



Cannabis and schizophrenia

Clinical Point

Some patients may be predisposed to substance-induced psychosis based on genetic variations and underlying brain structure changes

Box

Schizophrenia, cannabis, and brain changes

Schizophrenia is associated with several structural changes in the brain, including lateral ventriculomegaly, reduced prefrontal cortex volume, and generalized atrophy. These changes may precede illness and act as a risk marker.⁴ A multivariate regression analysis that compared patients with schizophrenia who were cannabis users vs patients with schizophrenia who were nonusers found that those with high-level cannabis use had relatively higher left and right lateral ventricle volume ($r = 0.208$, $P = .13$, and $r = 0.226$, $P = .007$, respectively) as well as increased third ventricle volume ($r = 0.271$, $P = .001$).⁴ These changes were dose-dependent and may lead to worse disease outcomes.⁴

acid. Certain positive symptoms, such as hallucinations, are uniquely human and difficult to study in animal models.⁵ Psychoactive substance use, especially cannabis, is frequently comorbid with schizophrenia. Additionally, certain individuals may be more predisposed to substance-induced psychosis than others based on genetic variation and underlying brain structure changes.⁴ Substance-induced psychosis is a psychotic state following the ingestion of a psychoactive substance or drug withdrawal lasting ≥ 48 hours.⁶ The psychoactive effects of cannabis have been associated with an exacerbation of existing schizophrenia symptoms.⁷ In 1998, Hall⁷ proposed 2 hypotheses to explain the relationship between cannabis and psychosis. The first was that heavy consumption of cannabis triggers a specific type of cannabis psychosis.⁷ The second was that cannabis use exacerbates existing schizophrenia, making the symptoms worse.⁷ Hall⁷ concluded that there was a complicated interaction among an individual's vulnerability to their stressors, environment, and genetics.

Cannabis, COMT, and homocysteine

Great advances have been made in our ability to examine the association between genetics and metabolism. One example of

this is the interaction between the catechol-O-methyltransferase (COMT) gene and the active component of cannabis, delta-9-tetrahydrocannabinol (THC). COMT codes for an enzyme that degrades cortical dopamine. The Val158Met polymorphism of this gene increases COMT activity, leading to increased dopamine catabolism, and thus decreased levels of extracellular dopamine, which induces an increase in mesolimbic dopaminergic activity, thereby increasing susceptibility to psychosis.³

In a study that genotyped 135 patients with schizophrenia, the Val158Met polymorphism was present in 29.63% of participants.³ Because THC can induce episodes of psychosis, individuals with this polymorphism may be at a higher risk of developing schizophrenia. Compared to Met carrier control participants with similar histories of cannabis consumption, those with the Val158Met polymorphism demonstrated markedly worse performance on tests of verbal fluency and processing speed.³ This is clinically significant because cognitive impairments are a major prognostic factor in schizophrenia, and identifying patients with this polymorphism could help personalize interventions for those who consume cannabis and are at risk of developing schizophrenia.

A study that evaluated 56 patients with first-episode schizophrenia found that having a history of cannabis abuse was associated with significantly higher levels of homocysteine as well as lower levels of high-density lipoprotein and vitamin B12.⁸ Homocysteine is an agonist at the glutamate binding site and a partial antagonist at the glycine co-agonist site in the *N*-methyl-D-aspartate receptor, which suggests that homocysteine may contribute to hypo-functioning of glutamate transmission; this is implicated in the development of schizophrenia. These increases in homocysteine are also found in siblings of patients with schizophrenia, which indicates a possible association between the methylenetetrahydrofolate (MTHFR) gene and schizophrenia.⁸

The C677T polymorphism in MTHFR may predict the risk of developing metabolic syndrome in patients taking second-generation

antipsychotics.⁸ Elevations in homocysteine by as little as 5 $\mu\text{mol/L}$ may increase schizophrenia risk by 70% compared to controls, possibly due to homocysteine initiating neuronal apoptosis, catalyzing dysfunction of the mitochondria, or increasing oxidative stress.⁸ There is a positive correlation between homocysteine levels and severity of negative symptoms ($P = .006$) and general psychopathology ($P = .008$) of schizophrenia when analyzed using the Positive and Negative Syndrome Scale.⁸ Negative symptoms such as blunted affect, apathy, anhedonia, and loss of motivation significantly impact the social and economic outcomes of patients diagnosed with schizophrenia.

Research paints a mixed picture

A Danish study analyzed the rates of conversion to schizophrenia or bipolar disorder (BD) among 6,788 individuals who received a diagnosis of substance-induced psychosis from 1994 to 2014.⁶ Ten comparison participants were selected for each case participant, matched on sex and year/month of birth. Participants were followed until the first occurrence of schizophrenia or BD, death, or emigration from Denmark. Substances implicated in the initial psychotic episode included cannabis, alcohol, opioids, sedatives, cocaine, amphetamines, hallucinogens, and combinations of substances.

The overall conversion rate over 20 years was 32.2% (95% CI, 29.7 to 34.9), with 26.0% developing schizophrenia vs 8.4% developing BD.⁶ Of the substances involved, cannabis was the most common, implicated in 41.2% (95% CI, 36.6 to 46.2) of cases.⁶ One-half of male patients converted within 2.0 years and one-half of female patients converted within 4.4 years after a cannabis-induced psychosis.⁶

This study had several limitations. It could not account for any short-term psychotic symptoms experienced by the general population, especially after cannabis use. Such patients might not seek treatment. Thus, the results might not be generalizable to the general population. The study did not evaluate if conversion rates differed based on continued substance use

following the psychosis episode, or the amount of each substance taken prior to the episode. Dose-dependence was not well elucidated, and this study only looked at patients from Denmark and did not account for socioeconomic status.⁶

Another Danish study looked at the influences of gender and cannabis use in the early course of the disease in 133 patients with schizophrenia.⁹ These researchers found that male gender was a significant predictor of earlier onset of dysfunction socially and in the workplace, as well as a higher risk of developing negative symptoms. However, compared to gender, cannabis use was a stronger predictor of age at first psychotic episode. For cannabis users, the median age of onset of negative symptoms was 23.7, compared to 38.4 for nonusers ($P < .001$).⁹

Cannabis use is significantly elevated among individuals with psychosis, with a 12-month prevalence of 29.2% compared to 4.0% among the general population of the United States.¹⁰ In a study that assessed 229 patients with a schizophrenia spectrum disorder during their first hospitalization and 6 months, 2 years, 4 years, and 10 years later, Foti et al¹⁰ found that the lifetime rate of cannabis use was 66.2%. Survival analysis found cannabis use doubled the risk of the onset of psychosis compared to nonusers of the same age (hazard ratio [HR] = 1.97; 95% CI, 1.48 to 2.62, $P < .001$), even after adjusting for socioeconomic status, age, and gender (HR = 1.34; 95% CI, 1.01 to 1.77, $P < .05$).¹⁰ Additionally, Foti et al¹⁰ found significant positive correlations between psychotic symptoms and cannabis use in patients with schizophrenia over the course of 10 years. An increase in symptoms was associated with a higher likelihood of cannabis use, and a decrease in symptoms was correlated with a lower likelihood of use (adjusted odds ratio = 1.64; 95% CI, 1.12 to 2.43, $P < .0125$).¹⁰

Ortiz-Medina et al¹¹ conducted a meta-analysis of 22 studies of 15 cohorts from healthy populations and 12 other cohort follow-up studies that evaluated the onset of psychotic symptoms in individuals who used cannabis. Most studies found associations between cannabis use and the onset

Clinical Point

One meta-analysis found repeated cannabis use increased the risk of developing psychotic symptoms



Cannabis and schizophrenia

Clinical Point

It may require a relatively high number of individuals to stop using cannabis to prevent 1 case of schizophrenia

of symptoms of schizophrenia, and most determined cannabis was also a major risk factor for other psychotic disorders. Analyses of dose-dependence indicated that repeated cannabis use increased the risk of developing psychotic symptoms. This risk is increased when an individual starts using cannabis before age 15.¹¹ Age seemed to be a stronger predictor of onset and outcome than sex, with no significant differences between men and women. One study in this review found that approximately 8% to 13% cases of schizophrenia may have been solely due to cannabis.¹¹ The most significant limitation to the studies analyzed in this review is that retrospective studies utilize self-reported questionnaires.

Other researchers have found it would take a relatively high number of individuals to stop using cannabis to prevent 1 case of schizophrenia. In a study of data from England and Wales, Hickman et al¹² evaluated the best available estimates of the incidence of schizophrenia, rates of heavy and light cannabis use, and risk that cannabis causes schizophrenia to determine the number needed to prevent (NNP) 1 case of schizophrenia. They estimated that it would require approximately 2,800 men age 20 to 24 (90% CI, 2,018 to 4,530) and 4,700 men age 35 to 39 (90% CI, 3,114 to 8,416) who heavily used cannabis to stop their consumption to prevent 1 case of schizophrenia.¹² For women with heavy cannabis use, the mean NNP was 5,470 for women age 25 to 29 (90% CI, 3,640 to 9,839) and 10,870 for women age 35 to 39 (90% CI, 6,786 to 22,732).¹² For light cannabis users, the NNP was 4 to 5 times higher than the NNP for heavy cannabis users. This suggests that clinical interventions aimed at preventing dependence on cannabis would be more effective than interventions aimed at eliminating cannabis use.

Medical cannabis and increased potency

In recent years, the use of medical cannabis, which is used to address adverse effects of chemotherapy as well as neuropathic pain, Parkinson's disease, and epilepsy, has been increasing.¹³ However, there is a lack

of well-conducted randomized clinical trials evaluating medical cannabis' efficacy and safety. As medical cannabis continues to gain public acceptance and more states permit its legal use, patients and physicians should be fully informed of the known adverse effects, including impaired attention, learning, and motivation.¹³

Several studies have drawn attention to the dose-dependence of many of cannabis' effects. Since at least the 1960s, the concentration of THC in cannabis has increased substantially, thus increasing its potency. Based on 66,747 samples across 8 studies, 1 meta-analysis estimated that THC concentrations in herbal cannabis increased by 0.29% ($P < .001$) each year between 1970 and 2017.¹⁴ Similarly, THC concentrations in cannabis resins were found to have increased by 0.57% ($P = .017$) each year between 1975 and 2017.¹⁴ Cannabis products with high concentrations of THC carry an increased risk of addiction and mental health disorders.¹⁴

Identifying those at highest risk

Despite ongoing research, scientific consensus on the relationship of cannabis to schizophrenia and psychosis has yet to be reached. The disparity between the relatively high prevalence of regular adult use of cannabis (8%⁷) and the low incidence of cannabis-induced psychosis suggests that cannabis use alone is unlikely to lead to episodes of psychosis in individuals who are not predisposed to such episodes. Sarrazin et al¹⁵ evaluated 170 patients with schizophrenia, 31 of whom had cannabis use disorder. They found no significant difference in lifetime symptom dimensions between groups, and proposed that cannabis-associated schizophrenia should not be categorized as a distinct clinical entity of schizophrenia with specific features.¹⁵

Policies that encourage follow-up of patients after episodes of drug-induced psychosis may mitigate the adverse social and economic effects of schizophrenia. Currently, these policies are not widely implemented in health care institutions, possibly because psychotic symptoms may fade after the drug's effects have dissipated.

Despite this, these patients are at high risk of developing schizophrenia and self-harm. New-onset schizophrenia should be promptly identified because delayed diagnosis is associated with worse prognosis.⁶ Additionally, identifying genetic susceptibilities to schizophrenia—such as the Val158Met polymorphisms—in individuals who use cannabis could help clinicians manage or slow the onset or progression of schizophrenia.³ Motivational interviewing strategies should be used to minimize or eliminate cannabis use in individuals with active schizophrenia or psychosis, thus preventing worse outcomes.

References

1. Simeone JC, Ward AJ, Rotella P, et al. An evaluation of variation in published estimates of schizophrenia prevalence from 1990-2013: a systematic literature review. *BMC Psychiatry*. 2015;15(1):193. doi:10.1186/s12888-015-0578-7
2. Tandon R, Gaebel W, Barch DM, et al. Definition and description of schizophrenia in the DSM-5. *Schizophr Res*. 2013;150(1):3-10. doi:10.1016/j.schres.2013.05.028
3. Bosia M, Buonocore M, Bechi M, et al. Schizophrenia, cannabis use and catechol-O-methyltransferase (COMT): modeling the interplay on cognition. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;92:363-368. doi:10.1016/j.pnpbp.2019.02.009
4. Welch KA, McIntosh AM, Job DE, et al. The impact of substance use on brain structure in people at high risk of developing schizophrenia. *Schizophr Bull*. 2011;37(5):1066-1076. doi:10.1093/schbul/sbq013
5. Winship IR, Dursun SM, Baker GB, et al. An overview of animal models related to schizophrenia. *Can J Psychiatry*. 2019;64(1):5-17. doi:10.1177/0706743718773728
6. Starzer MSK, Nordentoft M, Hjorthøj C. Rates and predictors of conversion to schizophrenia or bipolar disorder following substance-induced psychosis. *Am J Psychiatry*. 2018;175(4):343-350. doi:10.1176/appi.ajp.2017.17020223
7. Hall W. Cannabis use and psychosis. *Drug Alcohol Rev*. 1998;17(4):433-444. doi:10.1080/09595239800187271

Related Resources

- Khokhar JY, Dwiell LL, Henricks AM, et al. The link between schizophrenia and substance use disorder: a unifying hypothesis. *Schizophr Res*. 2018;194:78-85. doi:10.1016/j.schres.2017.04.016
- Otite ES, Solanky A, Doumas S. Adolescents, THC, and the risk of psychosis. *Current Psychiatry*. 2021;20(12):e1-e2. doi:10.12788/cp.0197

8. Misiak B, Frydecka D, Slezak R, et al. Elevated homocysteine level in first-episode schizophrenia patients—the relevance of family history of schizophrenia and lifetime diagnosis of cannabis abuse. *Metab Brain Dis*. 2014;29(3):661-670. doi:10.1007/s11011-014-9534-3
9. Veen ND, Selten J, van der Tweel I, et al. Cannabis use and age at onset of schizophrenia. *Am J Psychiatry*. 2004;161(3):501-506. doi:10.1176/appi.ajp.161.3.501
10. Foti DJ, Kotov R, Guey LT, et al. Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. *Am J Psychiatry*. 2010;167(8):987-993. doi:10.1176/appi.ajp.2010.09020189
11. Ortiz-Medina MB, Perea M, Torales J, et al. Cannabis consumption and psychosis or schizophrenia development. *Int J Soc Psychiatry*. 2018;64(7):690-704. doi:10.1177/0020764018801690
12. Hickman M, Vickerman P, Macleod J, et al. If cannabis caused schizophrenia—how many cannabis users may need to be prevented in order to prevent one case of schizophrenia? England and Wales calculations. *Addiction*. 2009;104(11):1856-1861. doi:10.1111/j.1360-0443.2009.02736.x
13. Gupta S, Phalen T, Gupta S. Medical marijuana: do the benefits outweigh the risks? *Current Psychiatry*. 2018;17(1):34-41.
14. Freeman TP, Craft S, Wilson J, et al. Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systematic review and meta-analysis. *Addiction*. 2021;116(5):1000-1010. doi:10.1111/add.15253
15. Sarrazin S, Louppe F, Doukhan R, et al. A clinical comparison of schizophrenia with and without pre-onset cannabis use disorder: a retrospective cohort study using categorical and dimensional approaches. *Ann Gen Psychiatry*. 2015;14:44. doi:10.1186/s12991-015-0083-x

Clinical Point

Cannabis use alone is unlikely to lead to episodes of psychosis in individuals who are not predisposed to such episodes

Bottom Line

Identifying susceptibilities to schizophrenia may guide interventions in patients who use cannabis. Several large studies have suggested that cannabis use may exacerbate symptoms and worsen the prognosis of schizophrenia. Motivational interviewing strategies aimed at minimizing cannabis use may improve outcomes in patients with schizophrenia.