

Does marijuana contribute to psychotic illness?

Cannabis abuse is not benign, especially in adolescents.

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Evidence grows that marijuana use can cause acute psychosis, bring forward in time a first schizophrenia episode, and worsen the prognosis of patients with psychotic disorders.

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Roger, age 16, had been smoking marijuana on and off for about 2 years. His parents knew but believed this was a stage and not dangerous; they had tried marijuana in their youth without harm. Roger's smoking had increased to several joints daily since he started a relationship with an older girl, who shared and encouraged his habit.

His parents became worried when Roger began making unusual comments, saying that food did not taste "right" and he thought someone was poisoning him. They brought Roger for psychiatric consultation at the recommendation of their family physician.

History and examination revealed that Roger had experienced vague persecutory ideas for several weeks but no systematized delusions or hallucinations. I told Roger and his parents he probably had a drug-induced psychosis and that symptoms would likely disappear without recurrence if he stopped using marijuana. At 2-weeks' follow-up, he described no more psychotic experiences and said he now realized the danger for him of smoking marijuana. A review 1 month later showed Roger was doing well, and I discharged him after reinforcing the importance of abstinence. But his case didn't end there.

Two years later, I received a request for information about Roger's episode from an acute inpatient facility. Roger had been admitted after an incident at the local mall in which he screamed at people and accused bystanders of trying to harm him. Despite using marijuana only occasionally, his behavior had been deteriorating and was becoming increasingly bizarre. The attending psychiatrist believed Roger had schizophrenia.

Clinicians regularly deal with patients such as Roger who suffer from a psychotic disorder and use marijuana. This is hardly surprising because marijuana is the most widely used illicit drug. In 2006, 5% of 12th graders in the United States reported using marijuana daily during the previous month, and 42% had tried it at least once.¹

Is psychotic patients' use of marijuana a coincidence? Self-medication? Or could cannabis cause psychotic illness? This debate elicits strong views among community and professional groups. To help you provide up-to-date advice to patients and families, this review:

- describes the growing body of evidence on the mental health consequences of marijuana use
- seeks to help you detect and deal with the effects of marijuana use in clinical practice.

MARIJUANA AND PSYCHOSIS

Although the neurobiologic association is unclear (Box 1),^{2,4} up to 15% of users report psychotic phenomena after consuming marijuana.⁵ Naturalistic and experimental studies have confirmed that marijuana can induce short-lived psychotic experiences.

In two parallel trials, 22 healthy individuals⁶ and 13 stable, antipsychotic-treated schizophrenia patients⁷ were given 2.5 mg and 5 mg intravenously of delta-9-tetrahydrocannabinol (delta-9-THC)—the primary psychoactive constituent of marijuana. Both groups developed dose-related, transient, schizophrenia-like symptoms and altered perceptions:

- Healthy volunteers showed the full range of psychotic symptoms. One individual said, "I thought you were giving me THC through the blood pressure machine and the sheets."²
- Schizophrenia patients tended to report increases in the symptoms of their specific conditions. Those with paranoid illnesses, for example, reported an escalation in persecutory ideas.

Transient psychotic phenomena are not equivalent to a psychotic illness, however. To meet diagnostic criteria for a psychotic disorder, symptoms must be persistent and impair psychosocial functioning.

Early reports. Anecdotal clinical reports that marijuana use could cause psychosis emerged in the 1960s but were largely ignored. Many clinicians assumed that psychotic individuals used marijuana to relieve troubling symptoms (self-medication).

A 15-year, longitudinal study examined the incidence of schizophrenia in >50,000 Swedish conscripts and concluded that marijuana use during adolescence increased the risk of schizophrenia.⁸ Skeptics questioned the validity of the diagnosis and the etiologic role of other drugs in this study and suggested that prodromal symptoms might have led to marijuana use, rather than marijuana triggering the psychosis.

Recent evidence. Better-designed studies have shown that marijuana use increases the risk of psychosis later in life.

Adolescents who used marijuana by age 15 were more likely to develop a schizophreniform disorder by age 26 than nonusers, according to data from 759 New Zealanders who took part in a prospective, longitudinal, general population study. Marijuana use by age 15 was associated with a higher risk than later use (by age 18).⁹

A 3-year, longitudinal, population-based study from the Netherlands found marijuana use associated with increased risk of psychosis in 4,045 previously psychosis-free individuals. More than 50% of psychosis diagnoses could be attributed to marijuana use.¹⁰

Data from the 21-year longitudinal Christchurch Health and Development Study in New Zealand showed elevated rates of psychotic symptoms in young people with cannabis dependence at ages 18 and 21. The associations remained even after adjustments were made for previous psychotic symptoms and other confounding factors.¹¹

Follow-up analysis of data from the Swedish military conscripts study⁸ showed that the use of other psychoactive drugs or prodromal cases in the cohort did not explain the association between self-reported marijuana use and hospital admissions for schizophrenia and other psychoses.¹²

Researchers in Israel cross-linked a cohort of 9,724 youths aged 16 to 17 screened by the Israeli Draft Board with a national registry of psychiatric hospital admissions for schizophrenia in the following 4 to 15 years. Self-reported drug abuse (mostly marijuana) was higher in adolescents who were later hospitalized for schizophrenia (12.4%) than in those not hospitalized (5.9%).¹³

Summary. A review of these 5 studies concluded that evidence supports the hypothesis that marijuana use acts as a risk factor in schizophrenia onset.¹⁴ Although marijuana use is not a “necessary” causal factor in psychotic illness—most users do not develop the disorder, and many persons with schizophrenia do not use marijuana—strong evidence indicates that it is one of many factors that can cause a psychotic illness (Box 2).⁹⁻¹⁴

WHO IS AT RISK?

Can marijuana cause psychosis in any person or specifically in those at increased risk of psychosis? If the latter, then marijuana—rather than causing new, unanticipated cases—might bring forward schizophrenia onset in individuals who would have developed it later. This explanation is consistent with data showing that persons born in more-recent cohorts seem to have an earlier age of schizophrenia onset.¹⁵

Vulnerability for psychosis. Evidence strongly suggests that marijuana-induced psychotic symptoms are more prevalent among vulnerable or psychosis-prone individuals.

- When given 2.5 mg of delta-9-THC, 80% of 13 patients with well-controlled schizophrenia experienced high Positive and Negative Syndrome Scale scores, compared with 35% of 22 healthy controls.²
- Unusual perceptions or thought influence were more common following marijuana use in all participants in a naturalistic experiment, but much more so in “at risk” individuals who had previously described isolated psychotic symptoms.¹⁶
- Adolescents and young adults ages 14 to 24 who used marijuana and displayed high “psychoticism” scores at baseline had more than twice the risk of a psychosis outcome 4 years later than did those without high scores.¹⁷

Schizophrenia onset. Marijuana users who suffer a drug-induced psychosis are at very high risk of developing a psychotic illness later on. A ≥3-year follow-up study¹⁸ of 535 patients who had not been treated for psychotic problems before being diagnosed with marijuana-induced psychotic symptoms found that:

- marijuana-induced psychotic episodes often remitted quickly with minimal treatment
- about one-half of patients were diagnosed with a schizophrenia-spectrum disorder (mostly paranoid schizophrenia) at follow up

- the gap between the marijuana-induced episode and diagnosis of a schizophrenia-spectrum disorder was >1 year in 47% of cases.
- the first episode of schizophrenia in these patients occurred several years earlier than in schizophrenia patients without marijuana-induced psychosis.

Although these findings require replication, they challenge the belief that marijuana-induced psychosis is benign (Box 3).

IMPLICATIONS FOR TREATMENT

Most psychiatric practitioners treat patients who have psychotic illness and use marijuana (Box 4). Compared with nonusers, these patients tend to have:

- earlier age of schizophrenia onset
- more psychotic symptoms
- worse prognosis because of poorer treatment adherence
- increased symptom severity and persistence
- higher relapse rates.¹⁹

Therefore, ask patients with psychotic disorders about their marijuana use, and treat both the marijuana use and the psychosis. Evidence to guide treatment is scarce, however. Nicotine, marijuana, and alcohol use are often intertwined. This suggests that treatments that target a variety of substances may be more efficient than targeted ones, even if the generic interventions are brief.²⁰

A study of marijuana users with early psychosis showed, for example, that marijuana-focused treatment was not more effective than psychoeducation, although both resulted in reduced use.²¹ In nonpsychotic individuals, giving 90 adult patients incentive vouchers to exchange for retail items each time they provided a marijuana-negative urine specimen resulted in increased abstinence rates over a 12-month period (Box 5).^{22,23} Cognitive-behavioral therapy helped to sustain the vouchers' positive effect on abstinence after the initial 14-week treatment.²³

Treatment with first-generation antipsychotics does not appear to decrease substance use. Several studies suggest that clozapine decreases the use of nicotine, alcohol, or other substances among patients with schizophrenia,²⁴ though this does not necessarily apply to other second-generation antipsychotics (Box 6).

IMPLICATIONS FOR PREVENTION

Psychiatric practitioners can play an important role in making young people aware of the mental health risks of using marijuana. Marijuana use fluctuates population-wide, depending in part on public perception of its harmfulness. Its use may diminish, therefore, as information on its mental health hazards percolates into high schools and the community at large. We also have the duty to make policy makers and legislators aware of this information.²⁵

Related resources

- National Institute on Drug Abuse. www.marijuana-info.org.
- Cannabis dependence. www.mentalhealth.com/dis/p20-sb03.html.
- Castle D, Murray R, eds. *Marijuana and madness: psychiatry and neurobiology*. Cambridge, UK: Cambridge University Press; 2004.
- Hall W, Pacula RL. *Cannabis use and dependence: public health and public policy*. Cambridge, UK: Cambridge University Press; 2003.

Drug brand names

Clozapine • Clozaril

Disclosure

Dr. Rey reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

References

1. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. *Teen drug use continues down in 2006, particularly among older teens; but use of prescription-type drugs remains high*. Ann Arbor, MI: University of Michigan News and Information Services; Dec. 21, 2006. Available at: <http://monitoringthefuture.org>. Accessed January 2, 2007.
2. D'Souza DC, Cho HS, Perry EB, Krystal JH. Cannabinoid 'model' psychosis, dopamine-cannabinoid interactions and implications for schizophrenia. In: Castle D, Murray R, eds. *Marijuana and madness: psychiatry and neurobiology*. Cambridge, UK: Cambridge University Press; 2004:142-65.
3. Caspi A, Moffitt TE, Cannon M, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol Psychiatry* 2005;57(10):1117-27.
4. Henquet C, Rosa A, Krabbendam L, et al. An experimental study of catechol-O-methyltransferase Val158 Met moderation of Δ -9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacol* 2006;31:2748-57.
5. Thomas H. A community survey of adverse effects of cannabis use. *Drug Alcohol Depend* 1996;42(3):201-7.
6. D'Souza DC, Perry E, MacDougall L, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 2004;29:1558-72.
7. D'Souza DC, Abi-Saab WM, Madonick S, et al. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry* 2005;57:594-608.
8. Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet* 1987;2(8574):1483-6.
9. Arseneault L, Cannon M, Poulton R, et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ* 2002;325(7374):1212-3.
10. van Os J, Bak M, Hanssen M, et al. Cannabis use and psychosis: a longitudinal population-based study. *Am J Epidemiol* 2002;156(4):319-27.
11. Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. *Psychol Med* 2003;33(1):15-21.
12. Zammit S, Allebeck P, Andreasson S, et al. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ* 2002;325(7374):1199-201.
13. Weiser M, Knobler HY, Noy S, Kaplan Z. Clinical characteristics of adolescents later hospitalized for schizophrenia. *Am J Med Genet* 2002;114:949-55.
14. Smit F, Bolier L, Cuijpers P. Cannabis use and the risk of later schizophrenia: a review. *Addiction* 2004;99(4):425-30.
15. Di Maggio C, Martinez M, Menard JF, et al. Evidence of a cohort effect for age at onset of schizophrenia. *Am J Psychiatry* 2001;158(3):489-92.
16. Verdoux H, Gindre C, Sorbara F, et al. Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study. *Psychol Med* 2003;33(1):23-32.
17. Henquet C, Krabbendam L, Spauwen J, et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ* 2005;330(7481):11-4.
18. Arendt M, Rosenberg R, Foldager L, et al. Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. *Br J Psychiatry* 2005;187:510-5.
19. Pencer A, Addington J, Addington D. Outcome of a first episode of psychosis in adolescence: a 2-year follow-up. *Psychiatry Res* 2005; 133(1):35-43.
20. McCambridge J, Strang J. The efficacy of single-session motivational interviewing in reducing drug consumption and perceptions of drug-related risk and harm among young people: results from a multi-site cluster randomized trial. *Addiction* 2004;99(1):39-52.
21. Edwards J, Elkins K, Hinton M, et al. Randomized controlled trial of a cannabis-focused intervention for young people with first-episode psychosis. *Acta Psychiatr Scand* 2006;114(2):109-17.
22. Lussier JP, Heil SH, Mongeon JA, et al. A meta-analysis of voucher-based reinforcement therapy for substance use disorders. *Addiction* 2006;101:192-203.

23. Budney AJ, Moore BA, Rocha HL, Higgins ST. Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence. *J Consult Clin Psychol* 2006;74(2):307–16.
24. Brunette MF, Drake RE, Xie H, et al. Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. *Schizophr Bull* 2006;32(4):637–43.
25. Hall W, Degenhardt L. What are the policy implications of the evidence on cannabis and psychosis? *Can J Psychiatry* 2006;51(9):566–74.

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Box 1

By what mechanisms does marijuana use cause psychosis?

The **dopaminergic effect** of cannabinoid receptors (such as CB1) may be one biologic mechanism, according to preliminary evidence. But the dopaminergic pathway might not be the most relevant mechanism, because the primary psychoactive constituent of marijuana—delta-9-tetrahydrocannabinol (delta-9-THC)—causes or increases psychotic symptoms in patients with schizophrenia despite treatment with dopamine receptor antagonists.²

Gene-environment interactions also appear to be relevant. A functional polymorphism in the catechol-O-methyltransferase (COMT) gene (COMT Val¹⁵⁸ Met) moderates the influence of cannabis use on developing psychosis, according to a birth cohort study of 803 New Zealanders. COMT valine¹⁵⁸ allele carriers were most likely to exhibit psychotic symptoms and develop schizophreniform disorder if they used cannabis during adolescence. This association did not apply to adult-onset cannabis use.³

Results were similar in a study in which 30 patients with a psychotic disorder, 12 relatives of patients with a psychotic disorder, and 32 healthy controls received delta-9-THC or placebo.⁴

Box 2

Risk factors for psychotic illness onset in marijuana users

- Starting marijuana use in adolescence
- Using cannabis often (weekly or daily) or for long periods
- Unusual, psychotic-like experiences (such as fleeting persecutory ideas or ideas of reference) or displaying high “psychoticism” on the self-report Symptom Checklist-90-R
- Family history of psychosis
- Prior cannabis-induced psychotic episode

Box 3

Cannabis and psychosis: 4 clinical pearls

- **Cannabis use** increases the risk of developing psychosis and is estimated to double the risk for later schizophrenia (5 to 10 new cases per 10,000 person-years)
- **The association** is not an artifact of confounding factors such as prodromal symptoms or concurrent use of other substances (including amphetamines)
- **The risk increases** with the frequency and length of use (a dose-effect relationship)
- **Self-medication** is not the connection between cannabis use and schizophrenia, according to empiric evidence

Source: References 9-14

Box 4

Cannabis-induced psychotic episode vs schizophrenia

Is the diagnosis worthwhile? Acute-phase cannabis-induced psychosis and schizophrenia have similar presentations, making differential diagnosis difficult. If their treatment also is similar, is it clinically meaningful to distinguish whether marijuana use or

schizophrenia triggered psychotic symptoms? The answer is yes, because:

- schizophrenia has a worse course and prognosis
- many patients with cannabis-induced psychosis do not develop schizophrenia.

Diagnostic clues. Some clinicians believe cannabis-induced psychosis is more likely than schizophrenia to feature:

- expansive mood
- derealization or depersonalization experiences
- visual hallucinations
- less overall severity.

Consider the course. The only way to differentiate the two disorders is to consider the illness course. Cannabis-induced psychotic episodes occur during periods of intoxication or withdrawal, tend to be short-lived, and usually respond well to treatment if the person abstains.

Up to one-half of patients with a cannabis-induced psychosis develop a schizophrenia-spectrum disorder. Monitoring them (such as at 6-month intervals) is important, therefore, because schizophrenia onset often occurs >12 months after the cannabis-induced psychosis.

Box 5

Voucher-based reinforcement: Stay clean, earn free movie passes

Efficacy. In voucher-based reinforcement therapy, patients receive vouchers or monetary incentives redeemable for goods and services, contingent on satisfying predetermined therapeutic goals. A meta-analysis²² showed this therapy model can produce better outcomes in substance use disorders, compared with control treatment.

Marijuana abstinence. A 12-month study of 90 cannabis-dependent adults²³ found that voucher-based reinforcement therapy could extend marijuana abstinence. During the 14 weeks of active treatment, participants could redeem vouchers for goods or services—such as movie passes, sports/hobby equipment, work materials, or vocational classes.

- Participants earned a voucher worth \$1.50 for the first negative specimen.
- Voucher values increased by \$1.50 for each consecutive negative specimen.
- Two consecutive negative specimens earned a \$10 bonus.
- Voucher values dropped back to \$1.50 if participants provided a cannabinoid-positive specimen or failed to submit a scheduled specimen. Values then could re-escalate according to the same schedule.

Box 6

Treating patients with comorbid schizophrenia and cannabis use

- **Ask about** marijuana use when evaluating all patients, particularly young ones
- **Educate patients** and, if appropriate, families about the risks of marijuana use. One way to do this without sounding judgmental or confrontational is to follow the principles of motivational interviewing
- **Treat both** the psychosis and the substance use
- **Generic interventions** that target drug use might be more effective than those specific to cannabis use because psychotic patients often abuse a variety of substances
- **Psychoeducation** might be as effective as cannabis-specific treatments
- **Abstinence-based vouchers** are a simple intervention with some evidence of effectiveness
- **Clozapine**, which seems to reduce relapse of substance use in these patients, might be the antipsychotic of choice