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SPECIAL ARTICLE

Cannabis use and the risk of developing a psychotic disorder

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We briefly review the evidence that cannabis use in adolescence and young adulthood is a contributory cause of schizophreniform psychoses, by summarising longitudinal studies that: a) have examined relationships between cannabis use and the risk of psychosis or psychotic symptoms; and b) have controlled for potential confounders, such as other forms of drug use and personal characteristics that predict an increased risk of psychosis. There is now reasonable evidence from longitudinal studies that regular cannabis use predicts an increased risk of schizophrenia and of reporting psychotic symptoms. These relationships have persisted after controlling for confounding variables such as personal characteristics and other drug use. The relationships did not seem to be explained by cannabis being used to self-medicate symptoms of psychosis. A contributory causal relationship is biologically plausible because psychotic disorders involve disturbances in the dopamine neurotransmitter system with which the cannabinoid system interacts, as has been shown by animal studies and a human provocation study. We briefly explore the clinical and public health implications of the most plausible hypothesis, that cannabis use precipitates schizophrenia in persons who are vulnerable because of a personal or family history of schizophrenia.

Key words: Cannabis, psychosis, schizophrenia, adolescents, dopamine, educational interventions

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Regular cannabis use and psychotic disorders (such as schizophrenia) are associated in the general population (1,2), and heavy cannabis users are over-represented among new cases of schizophrenia (3-5). These findings, and rising rates of cannabis use among young people in many developed countries, have prompted debates about whether cannabis use may be a contributory cause of psychosis, that is, it may precipitate schizophrenia in vulnerable individuals. This hypothesis assumes that cannabis use is one factor among many others (including genetic predisposition and other unknown causes) that together cause schizophrenia.

There are also other possible explanations of the association. Common factors may increase the risk of cannabis use and psychosis, without the two being directly related. Cannabis could also be used to self-medicate the symptoms of schizophrenia (6-15).

The consistent finding of an association between cannabis use and psychosis makes chance an unlikely explanation of the association, and there are also now a number of prospective studies showing that cannabis use often precedes psychosis. The more difficult task has been excluding the hypothesis that the relationship is due to other factors, such as other drug use or a genetic predisposition to develop schizophrenia and use cannabis.

LONGITUDINAL STUDIES

The strongest evidence that cannabis use is a contributory cause of schizophrenia comes from longitudinal studies of large representative samples of the population who have been followed over time to see if cannabis users are at higher risk of developing schizophrenia. The earliest such study was a 15-year prospective investigation of cannabis use and schizophrenia in 50,465 Swedish conscripts. The study found that those who had tried cannabis by age 18 were 2.4 times more likely to be diagnosed with schizophrenia than those who had not (16) and the risk of this diagnosis increased with the frequency of cannabis use. The risks were substantially reduced but still significant after statistical adjustment for variables that were related to the risk of developing schizophrenia.

Zammit et al (17) reported a 27-year follow-up of the Swedish cohort that also found a dose-response relationship between frequency of cannabis use at baseline and risk of schizophrenia during the follow-up. The relationship between cannabis use and schizophrenia persisted when the authors statistically controlled for the effects of other drug use and other potential confounding factors, including a history of psychiatric symptoms at baseline. Assuming a causal relationship, and given current patterns of use, they estimated that 13% of cases of schizophrenia could be averted if all cannabis use were prevented.

Zammit et al's findings have been supported in a three-year longitudinal study of the relationship between self-reported cannabis use and psychosis in a community sample of 4,848 people in the Netherlands (18). Van Os et al found that cannabis use at baseline predicted an increased risk of psychotic symptoms during the follow-up period in individuals who had not reported these symptoms at baseline. There was a dose-response relationship between frequency of cannabis use at baseline and risk of psychotic symptoms during the follow-up period. This relationship persisted when they statistically controlled for the effects of other drug use, and it was stronger for cases with more severe psychotic symptoms. Individuals who reported any psychotic

symptoms at baseline were more likely to develop schizophrenia if they used cannabis than were individuals who were not so vulnerable.

These findings have been replicated in one German and two New Zealand cohort studies. Henquet et al (19) reported a 4-year follow-up of a cohort of 2,437 adolescents and young adults between 1995 and 1999 in Munich. They found a dose-response relationship between self-reported cannabis use at baseline and the likelihood of reporting psychotic symptoms at follow-up. Young people who reported psychotic symptoms at baseline were much more likely to experience psychotic symptoms at follow-up if they used cannabis.

Arseneault et al (20) reported a prospective study of young adults in a New Zealand birth cohort (n=759) whose members had been assessed on risk factors for psychotic symptoms and disorders since birth. They found a relationship between cannabis use by age 15 and an increased risk of psychotic symptoms by age 26. So too did Fergusson et al (21) in a longitudinal study of the relationship between cannabis dependence at age 18 and psychotic symptoms at age 21 in the Christchurch Health and Development Study birth cohort of 1,265 children. They found that cannabis dependence at age 18 predicted an increased risk of psychotic symptoms at age 21 (relative risk, RR=2.3). This association was smaller but still significant after adjustment for potential confounders (RR=1.8).

French researchers studied the relationship between cannabis use and psychotic symptoms using an "experience sampling method" (22). These investigators asked 79 college students to report on their drug use and psychotic symptoms at randomly selected time points, several times each day over 7 consecutive days. The students gave their ratings after being prompted to do so by a signal sent to a portable electronic device. High cannabis users (n=41) and students identified as vulnerable to psychosis (n=16) were over-represented. In time periods when cannabis was used, users reported more unusual perceptions, and vulnerable individuals who used cannabis were more likely to report strange impressions and unusual perceptions than individuals who lacked this vulnerability. There was no relationship between reporting unusual experiences and using cannabis, as would be expected if self-medication were involved.

Moore et al (23) reported a meta-analysis of six major longitudinal studies of the relationship between cannabis use and psychosis. They found an increased risk (odds ratio, OR=1.4; 95% confidence interval, CI: 1.20, 1.65) of psychotic disorder if someone ever used cannabis. There was also a dose-response relationship between self-reported frequency of cannabis use and the risk of subsequently developing psychotic symptoms or a psychotic disorder (OR=2.09; 95% CI: 1.54, 2.84). They argued that reverse causation had been better controlled in the majority of these studies (by either excluding cases reporting psychotic symptoms at baseline or by statistically adjusting for pre-existing psychotic symptoms). In all studies the association between cannabis use and psychosis was attenuated after statistical adjustment for potential confounders.

THE EFFECTS OF CANNABIS USE ON THE INCIDENCE OF PSYCHOSIS

Given this evidence, has the incidence of schizophrenia, particularly early-onset acute cases, changed during the 1970s and 1980s, when there have been very substantial increases in cannabis use among young adults in Australia and North America? A study modelling trends in the incidence of psychoses in Australia did not find clear evidence of any increase in incidence following steep increases in cannabis use during the 1980s (24). A more recent modelling study in the UK (25) suggested that it may be too early to detect any effect of cannabis use on the incidence of psychoses, because rates of cannabis use only increased during the 1990s in that country. A recent British (26) and a Swiss study (27) reported suggestive evidence of an increased incidence of psychoses among males in recent birth cohorts with the highest rates of cannabis use in adolescence. This work needs to be replicated in future research.

BIOLOGICAL PLAUSIBILITY

The dopaminergic system has long been considered to play an important role in psychotic disorders (28), but there is increasing evidence that the cannabinoid system may also be involved (29-32). The following types of evidence strongly suggest that a contributory causal role for cannabis in psychoses is biologically plausible.

First, elevated levels of anandamide, an endogenous cannabinoid agonist, have been found in the cerebrospinal fluid of persons with schizophrenia (33). A case-control study found that persons with schizophrenia had a greater density of CB_1 receptors in the prefrontal cortex than controls (34).

Second, an interaction has been reported between cannabis use and the catechol-O-methyl transferase (COMT) $Val^{158}Met$ polymorphism (35). Alterations in catecholamine, particularly dopamine, metabolism have been well documented among persons with schizophrenia and other schizophreniform disorders (36). The COMT functional polymorphism is a methylation enzyme that is important for the metabolism of dopamine (37).

Third, there is evidence from older retrospective (see 38) and more recently from prospective studies of recent onset cases of schizophrenia that regular cannabis use exacerbates the symptoms of the disorder (39-41). Prospective studies that have controlled for the effects of medication noncompliance (39,40) suggest that the relationship is not explained in this way. D'Souza et al (42,43) have found that intravenous tetrahydrocannabinol (THC) given under double-blind placebo control conditions produces dose-dependent increases in positive and negative psychotic symptoms in healthy volunteers and patients with schizophrenia in remission.

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A PUBLIC HEALTH CASE FOR PRUDENCE

Given residual uncertainties about the evidence for a causal relation between cannabis and psychosis, we need to consider the possible costs and benefits of different policy actions. This suggests that it is good policy to encourage young individuals to avoid using cannabis or at least to delay such use until early adulthood (44). If the relation is truly causal, the public health gain (a reduction in schizophrenia incidence) would arguably offset the foregone pleasure among those young individuals who either did not use cannabis or delayed using it until young adulthood. This argument makes a good case for discouraging cannabis use among young individuals, but it leaves room for disagreement about the best method of achieving this goal in particular population groups. It is to these latter questions that we now turn.

RESPONDING TO CANNABIS USE AMONG PEOPLE WITH PSYCHOSES

There is reasonable evidence that individuals with psychoses who are regular cannabis users have more positive symptoms, more frequent relapses, and require more hospitalization (41,45). It is accordingly wise to encourage young people with psychotic symptoms who use cannabis to stop or, at the very least, to encourage them reduce their frequency of use.

The major challenges lie in finding ways to persuade individuals with schizophrenia to stop doing something they enjoy and to help those who want to stop using cannabis but find it difficult to do so. Recent evaluations of psychological interventions for cannabis dependence in individuals without psychoses report modest rates of abstinence at the end of treatment (20 to 40%) and substantial rates of relapse thereafter (46). Many individuals with schizophrenia have characteristics that predict a poor outcome: they lack social support, they may be cognitively impaired, they are often unemployed, and they do not comply with treatment (47-49). A recent Cochrane review (50) found no clear evidence that supported any type of substance abuse treatment in schizophrenia over standard care. The development of more effective pharmacologic and psychological methods of treatment for cannabis dependence should be a research priority (29).

INFORMING YOUNG PEOPLE ABOUT THE MENTAL HEALTH RISKS OF CANNABIS USE

Finding effective ways of explaining the psychotogenic effects of cannabis use to young individuals is a major public health challenge. Young people also need to be informed about the risks of becoming dependent on cannabis, impairing their educational achievement, and increasing their risk of depression (51,52). These risks have often been overshadowed in the public debate about cannabis use, yet add weight to the argument for discouraging cannabis use among young individuals.

CONCLUSIONS

Regular cannabis use predicts an increased risk of schizophrenia, and the relationship persists after controlling for confounding variables. The relationship is unlikely to be explained by self-medication. There is increasing evidence that the association is biologically plausible, but given the complex nature of the aetiology of schizophrenia and related disorders, it is unlikely that the relationship will be due to an interaction between cannabis use and a single gene. Uncertainty about the biological mechanisms should not distract us from using educational, psychological and social interventions to reduce the use of cannabis by vulnerable young people and thereby the risk of problems related to its use (53).

References

1. Degenhardt L, Hall WD. The association between psychosis and problematical drug use among Australian adults: findings from the National Survey of Mental Health and Well-being. Psychol Med 2001;31:659-68.
2. Tien AY, Anthony JC. Epidemiological analysis of alcohol and drug use as risk factors for psychotic experiences. J Nerv Ment Dis 1990;178:473-80.
3. Barbee JG, Clark PD, Crapanzo MS et al. Alcohol and substance abuse among schizophrenic patients presenting to an emergency psychiatry service. J Nerv Ment Dis 1989;177:400-17.
4. Cohen M, Klein DF. Drug abuse in a young psychiatric population. Am J Orthopsychiatry 1970;40:448-55.
5. Wheatley M. The prevalence and relevance of substance use in detained schizophrenic patients. J Forensic Psychiatry 1998;9:114-29.
6. Mueser KT, Drake RE, Wallach MA. Dual diagnosis: a review of etiological theories. Addict Behav 1998;23:717-34.
7. Blanchard J, Brown S, Horan W et al. Substance use disorders in schizophrenia: review, integration, and a proposed model. Clin Psychol Rev 2000;20:207-34.
8. Rosenthal R. Is schizophrenia addiction prone? Curr Opin Psychiatry 1998;11:45-8.
9. Batel P. Addiction and schizophrenia. Eur Psychiatry 2000;15:115-22.
10. Gruber AJ, Pope HG. Cannabis psychotic disorder: does it exist? Am J Addict 1994;3:72-83.
11. Thornicroft G. Cannabis and psychosis: is there epidemiological evidence for an association? Br J Psychiatry 1990;157:25-33.
12. Hall WD. Cannabis use and psychosis. Drug Alcohol Rev 1998; 17:433-44.
13. Hall WD, Degenhardt L. Cannabis use and psychosis: a review of clinical and epidemiological evidence. Aust N Zeal J Psychiatry 2000;34:26-34.
14. McKay DR, Tennant CC. Is the grass greener? The link between cannabis and psychosis. Med J Aust 2000;172:284-6.
15. Phillips P, Johnson S. How does drug and alcohol misuse develop among people with psychotic illnesses? A literature review. Soc Psychiatry Psychiatr Epidemiol 2001;36:269-76.
16. Andreasson S, Engstrom A, Allebeck P et al. Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. Lancet 1987;2:1483-6.

17. 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;325:1199-201.
18. van Os J, Bak M, Hanssen M et al. Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol 2002;156: 319-27.
19. Henquet C, Krabbendam L, Spauwen J et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ 2004;330:11.
20. Arseneault L, Cannon M, Poulton R et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 2002;325:1212-3.
21. Fergusson DM, Horwood JL, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. Psychol Med 2003;33:15-21.
22. Verdoux H, Gindre C, Sorbara F et al. Cannabis use and the expression of psychosis vulnerability in daily life. Eur Psychiatry 2002;17:180S.
23. Moore TH, Zammit S, Lingford-Hughes A et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007;370:319-28.
24. Degenhardt L, Hall WD, Lynskey MT. Testing hypotheses about the relationship between cannabis use and psychosis. Drug Alcohol Depend 2003;71:37-48.
25. Hickman M, Vickerman P, Macleod J et al. Cannabis and schizophrenia: model projections of the impact of the rise in cannabis use on historical and future trends in schizophrenia in England and Wales. Addiction 2007;102:597-606.
26. Boydell J, van Os J, Caspi A et al. Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999. Psychol Med 2006;36:1441-6.
27. Ajdacic-Gross V, Lauber C, Warnke I et al. Changing incidence of psychotic disorders among the young in Zurich. Schizophr Res 2007;95:9-18.
28. Julien R. A primer of drug action: a concise, nontechnical guide to the actions, uses, and side effects of psychoactive drugs, 9th ed. New York: Freeman, 2001.
29. Ujike H, Morita Y. New perspectives in the studies on endocannabinoid and cannabis: cannabinoid receptors and schizophrenia. J Pharmacol Sci 2004;96:376-81.
30. Fritzsche M. Are cannabinoid receptor knockout mice animal models for schizophrenia? Med Hypotheses 2001;56:638-43.
31. Glass M. The role of cannabinoids in neurodegenerative diseases. Prog Neuropsychopharmacol Biol Psychiatry 2001;25:743-65.
32. Skosnik PD, Spatz-Glenn L, Park S. Cannabis use is associated with schizotypy and attentional dysinhibition. Schizophr Res 2001;48:83-92.
33. Leweke FM, Giuffrida A, Wurster U et al. Elevated endogenous cannabinoids in schizophrenia. Neuroreport 1999;10:1665-9.
34. Dean B, Sundram S, Bradbury R et al. Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. Neuroscience 2001;103:9-15.
35. 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;57:1117-27.
36. Bilder R, Volavka J, Lachman H et al. The catechol-O-methyltransferase (COMT) polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology 2004;29:1943-61.
37. Mannisto P, Kaakkola S. Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. Pharmacol Rev 2006; 51:593-628.
38. Hall WD, Degenhardt L. Is there a specific 'cannabis psychosis'? In: Castle DJ, Murray RM (eds). Marijuana and madness. Cambridge: Cambridge University Press, 2004:89-100.
39. Degenhardt L, Tennant C, Gilmour S et al. The temporal dynamics of relationships between cannabis, psychosis and depression among young adults with psychotic disorders: findings from a 10-month prospective study. Psychol Med 2007;37:927-34.
40. Hides L, Dawe S, Kavanagh DJ et al. Psychotic symptom and cannabis relapse in recent-onset psychosis. Prospective study. Br J Psychiatry 2006;189:137-43.
41. Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry 1994;51:273-9.
42. 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.
43. D'Souza DC, Cho HS, Perry E et al. Cannabinoid 'model' psychosis, dopamine-cannabinoid interactions and implications for schizophrenia. In: Castle DJ, Murray RM (eds). Marijuana and madness. Cambridge: Cambridge University Press, 2004:142-65.
44. de Irala J, Ruiz-Canela M, Martinez-Gonzalez MA. Causal relationship between cannabis use and psychotic symptoms or depression. Should we wait and see? A public health perspective. Med Sci Monit 2005;11:RA355-8.
45. Grech A, Van Os J, Jones PB et al. Cannabis use and outcome of recent onset psychosis. Eur Psychiatry 2005;20:349-53.
46. Roffman RA, Stephens RS. Cannabis dependence: its nature, consequences and treatment. Cambridge: Cambridge University Press, 2006.
47. Kavanagh DJ. An intervention for substance abuse in schizophrenia. Behav Change 1995;12:20-30.
48. Mueser KT, Bellack AS, Blanchard JJ. Comorbidity of schizophrenia and substance abuse: implications for treatment. J Consult Clin Psychol 1992;60:845-56.
49. Drake RE, Mueser KT, Brunette MF. Management of persons with co-occurring severe mental illness and substance use disorder: program implications. World Psychiatry 2007;6:131-6.
50. Jeffery DP, Ley A, McLaren S et al. Psychosocial treatment programmes for people with both severe mental illness and substance misuse. Cochrane Database Syst Rev 2000;Issue 2:CD001088.
51. Hall W. The mental health risks of adolescent cannabis use. PLoS Med 2006;3:159-62.
52. Patton GC, Coffey C, Carlin JB et al. Cannabis use and mental health in young people: cohort study. BMJ 2002;325:1195-8.
53 Hall WD, Degenhardt L. What are the policy implications of the evidence on cannabis and psychosis? Can J Psychiatry 2006;51:566-74.