In Review

Is Cannabis Use a Contributory Cause of Psychosis?

Louisa Degenhardt, MPsych(Clinical), PhD[1], Wayne Hall, PhD[2]

Objective: To assess whether cannabis use in adolescence and young adulthood is a contributory cause of schizophreniform psychosis in that it may precipitate psychosis in vulnerable individuals.

Method: We reviewed longitudinal studies of adolescents and young adults that examined the relations between self-reported cannabis use and the risk of diagnosis with a psychosis or of reporting psychotic symptoms. We also reviewed studies that controlled for potential confounders, such as other forms of drug use and personal characteristics that predict an increased risk of psychosis. We assessed evidence for the biological plausibility of a contributory causal relation.

Results: Evidence from 6 longitudinal studies in 5 countries shows that regular cannabis use predicts an increased risk of a schizophrenia diagnosis or of reporting symptoms of psychosis. These relations persisted after controlling for confounding variables, such as personal characteristics and other drug use. The relation did not seem to be a result of cannabis use to self-medicate symptoms of psychosis. A contributory causal relation is biologically plausible because psychotic disorders involve disturbances in the dopamine neurotransmitter systems with which the cannabinoid system interacts, as demonstrated by animal studies and one human provocation study.

Conclusion: It is most plausible that cannabis use precipitates schizophrenia in individuals who are vulnerable because of a personal or family history of schizophrenia.

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Highlights

- This review summarizes recent key prospective studies that provide consistent evidence that cannabis use may be a contributory cause of psychosis.
- It also synthesizes these studies in light of other evidence on the biological plausibility of the association.
- The clinical, regulatory, and policy implications of the evidence are discussed in the companion paper to this review (Hall and Degenhardt, Can J Psychiatry 2006;51:566–74).

Key Words: *cannabis, psychosis, schizophrenia, comorbidity, drug-induced psychosis, marijuana*

Over the past few decades, there has been growing evidence for an association between regular cannabis use and psychotic symptoms and disorders, both in the general population (1,2) and among incident cases of schizophrenia and other psychoses (3–5). This association prompts the question, Is cannabis use a contributory cause of psychosis?

It is useful to distinguish 2 ways in which cannabis use could cause psychosis (6). The strongest hypothesis is that heavy cannabis use causes a psychosis that would not have occurred in the absence of cannabis. A second, weaker hypothesis is that cannabis use is a contributory cause in the sense that it may precipitate schizophrenia in individuals vulnerable to the

illness. The second hypothesis assumes that cannabis use is one factor among many others (including genetic predisposition and other unknown causes) that act together to cause schizophrenia.

These are not the only possible explanations of the association (6–15). It is possible that cannabis use and psychosis are caused by common factors that increase the risk of both, or that individuals with schizophrenia use cannabis to self-medicate the symptoms of their disorder.

To infer that cannabis use causes psychosis in any of these ways, we need evidence of several things: an association between cannabis use and psychosis, that this association is greater than expected by chance, that cannabis use precedes psychosis, and that we can exclude plausible alternative explanations of this association (16). Evidence of the association between cannabis use and psychosis, as well as evidence that chance is an unlikely factor in this association, is readily available. Several prospective studies also show that cannabis use precedes psychosis. The difficulty lies in excluding the hypothesis that the relation between cannabis use and psychosis is due to other factors (for example, other drug use or a genetic predisposition to develop schizophrenia and subsequently use cannabis to self-medicate).

Cannabis as a Cause of Psychosis

A Specific Cannabis Psychosis

There are case reports of cannabis psychoses (17–21) describing individuals who develop psychotic disorders after using cannabis (22). These disorders have been attributed to cannabis use for combinations of the following reasons: the onset of the disorders followed the use of large quantities of cannabis; the affected individuals were confused, disorientated, and amnesic; some individuals had no personal or family history of psychosis; some individuals' symptoms remitted within days to weeks of enforced abstinence from cannabis; some individuals recovered completely and had no residual psychotic symptoms like those consistent with schizophrenia; and if the disorder recurred, it was only after the individual resumed cannabis use (6). Some commentators have criticized these case reports because they provide poor information on cannabis use and its relation to the onset of psychosis, the individual's premorbid adjustment, and the family history of psychosis (11,12). A recent retrospective study of Danish clinical registers found that most individuals with clinician-diagnosed, cannabis-induced psychotic disorders were subsequently diagnosed with schizophrenia or another psychotic disorder (21).

Abbreviations used in this article

COMT	catechol-O-methyltransferase
ECA	Epidemiologic Catchment Area studyI
NSMHWB	National Survey of Mental Health and Well-Being
RR	relative risk
SCL-90	Symptom Checklist, 90-item
THC	delta-9-tetrahydrocannabinol

Psychotic Symptoms and Cannabis Use

It is possible that cannabis use might trigger symptoms of psychosis among some users. This is distinct from a specific psychotic disorder attributable to cannabis use. Other drugs, such as amphetamines, also have the potential to trigger psychotic symptoms among some users (23). This possibility is also biologically plausible given the increasing evidence about the nature of the effects of cannabis on the brain (see discussion below). One study used an experimental design (as was used in the 1960s with amphetamines; 23) to show that intravenously administering THC to healthy volunteers without psychosis increased positive and negative psychotic symptoms in a dose-dependent way (24). It is important to note that effects on symptoms are clinically (and importantly) distinct from a psychotic disorder such as schizophrenia.

Several studies examined the relation between cannabis use and psychotic symptoms in the general population. Tien and Anthony used data from the ECA to examine correlates of reporting one or more psychotic experiences (that is, 4 types of hallucinations and 7 types of delusional beliefs), using a case–control design (2). They compared 477 individuals who reported one or more of these symptoms in a 1-year follow-up with 1818 control subjects who did not. Participants were matched for age and social and demographic characteristics. They found that daily cannabis use doubled the risk of reported psychotic symptoms (after statistical adjustment for alcohol use and psychiatric diagnoses at baseline).

Thomas reported the prevalence of psychotic symptoms among cannabis users in a random sample of individuals drawn from the electoral roll of a large city in the North Island of New Zealand (25). After using cannabis, 1 in 7 (14%) individuals reported strange, unpleasant experiences, such as hearing voices, having fears of persecution, or worrying that someone was attempting to harm them (25).

Stefanis and others reported cross-sectional relations between self-reported cannabis use and positive and negative symptoms of psychosis at age 18 years in a cohort of 3500 Greek adolescents (26). The rate of cannabis use was low, with only 6% reporting lifetime use and 0.9% reporting daily or near daily use. Nonetheless, they found positive associations between frequency of cannabis use (never, once, 2 to 4 times, 5 times or more, and daily or near daily) and 4 dimensions of psychotic experiences (paranoid, first rank, hallucinations, and grandiose experiences). These relations were not affected

Table 1 Summary of recent longitudinal studies examining the relation between cannabis and psychosis

Study	Participants	Drug measures	Psychosis measures	Main findings
Christchurch (54)	Study of young adults aged 18 to 21 years in Christchurch	Cannabis dependence according to DSM-IV criteria	Assessed with 10 items from the SCL-90	Dependence at age 18 years predicted increased risk of psychotic symptoms at age 21 years, after controlling for other factors such as other drug use and other psychiatric disorders
Dunedin (53)	Analysis of data from a birth cohort in New Zealand (*n* = 759)	Self-reported cannabis use	Assessed according to DSM-IV criteria; symptoms assessed at age 11 years; also looked at functional polymorphism of COMT gene that codes for dopamine and risk of psychosis	25% who were homozygous for a polymorphism and used cannabis were much more likely to develop schizophreniform disorders than those with a polymorphism who did not use cannabis; in the absence of a polymorphism, those who used cannabis were not at increased risk of psychosis
Stefanis (26)	3500 Greek adolescents aged 18 years	Self-reported cannabis use and frequency of cannabis use: never, once, 2 to 4 times, > 5 times, daily or near daily use	Paranoia, first rank, hallucinations, grandiose experiences	Positive association found between frequency of cannabis use and psychotic measures, after controlling for other drug use and depressive symptoms; association stronger for those reporting initiation of cannabis use before age 15 years
van Os (50)	Study over 3 years of 4848 people drawn from a community in The Netherlands	Self-reported cannabis and other drug use at baseline and follow-up, as well as frequency of use	Assessed by computerized diagnostic interview at baseline and follow-up	Cannabis use at baseline predicted increased risk of psychotic symptoms at follow-up; the greater the frequency of use at baseline, the greater the risk of psychotic symptoms at follow-up; relation remained when other drug use was controlled for; relation stronger for those with more severe psychotic symptoms
Henquet (51)	Study over 4 years of 2437 adolescents and young adults in Munich	Self-reported cannabis use at baseline and follow-up, as well as frequency of cannabis use	Assessed in early adulthood with the Computerized Composite International Diagnostic Interview at baseline and follow-up	Dose–response relation found between cannabis use at baseline and likelihood of reporting psychotic symptoms; those with psychotic symptoms at baseline were more likely to report symptoms at follow-up if they used cannabis than were those who did not use cannabis

Table 1 continued

Study	Participants	Drug measures	Psychosis measures	Main findings
Ferdinand (61)	Study over 14 years of 1580 adolescents and young adults in The Netherlands	Self-reported cannabis use	Assessed using the Computerized Composite International Diagnostic Interview	Findings indicate bidirectional relation between cannabis use and psychosis; early cannabis use predicted psychotic symptoms after adjusting for preexisting psychopathology; psychotic symptoms in those who had not used cannabis before the onset of psychotic symptoms predicted future cannabis use
Zammit (49)	Study over 27 years of individuals aged 18 to 20 years	Self-reported cannabis use and frequency of use	Schizophrenia assessed according to DSM-IV criteria	Cannabis use at baseline predicted increased risk of schizophrenia at follow-up, after controlling for other drug use and potential confounders; the more frequent the cannabis use at baseline, the greater the risk of schizophrenia at follow-up

by controlling for other drug use or symptoms of depression. They were also stronger in individuals who reported initiation of cannabis use prior to age 15 years.

Community surveys of psychiatric disorders, such as the ECA, have reported higher rates of substance use disorders among individuals with schizophrenia (27). Nearly one-half of the patients identified in the ECA as having schizophrenia were also diagnosed with substance abuse or dependence (34% for an alcohol disorder and 28% for another drug disorder) (28). These rates were higher than those among the general population, which were 14% for alcohol disorders (29) and 6% for drug abuse (27). The most common patterns of substance use among the 231 individuals with schizophrenia in the ECA were alcohol (37%) and cannabis (23%), stimulants and hallucinogens (13%), and narcotics (10%) and sedatives (8%) (30).

The NSMHWB, conducted in Australia in 1997, included a screening questionnaire for psychotic symptoms (31). Among those under age 50 years who screened positive for a psychotic disorder, 7.8% ($n = 27$) met ICD-10 criteria for cannabis dependence in the past 12 months. This was 17.2% of all individuals diagnosed with cannabis dependence. A diagnosis of cannabis dependence made the chances of reporting psychotic symptoms 1.71 times more likely, after adjusting for age, affective and anxiety disorders, smoking status, and alcohol dependence (1). In the NSMHWB, 11.5% of individuals who reported being diagnosed with schizophrenia met ICD-10 criteria for a cannabis use disorder in the prior 12 months, and 21.2% met criteria for an alcohol use disorder. After adjusting for confounding variables, those who met criteria for cannabis dependence were 2.9 times more likely to report that they had been diagnosed with schizophrenia than those who did not.

Cannabis Use and Schizophrenia

Clinical Studies

In case–control studies, patients with schizophrenia are more likely to use cannabis than other psychiatric patients or control subjects without schizophrenia (32–34). The prevalence of cannabis use in patients with schizophrenia varies among studies, but it is generally higher than the rates in the general population (34,35). These variations are probably owing to differences in the sampling of patients, with younger individuals reporting higher rates of cannabis use than older individuals with chronic disorders. After alcohol and tobacco, cannabis is the most commonly used drug, and it is often used with alcohol (36,37).

Apart from finding that young men are overrepresented among cannabis users (6), as they are in the general community (38), the controlled clinical studies provide conflicting evidence on the correlates of substance abuse in schizophrenia. In some studies, cannabis users had an earlier onset of

psychotic symptoms, a better premorbid adjustment, more episodes of illness, and more hallucinations (36,39–42). Other controlled studies failed to replicate some of these findings (30,43–46).

A recent clinical study adopted a novel approach to studying the relation between cannabis use and psychosis (47). In this study, 100 young individuals (49% male with an average age of 19.3 years) were identified as being at ultra high risk of psychosis on the basis of one or more criteria: schizophrenia in a first-degree relative, the presence of attenuated psychotic symptoms, or a brief, limited psychosis. Cannabis was the most commonly used drug in the 12 months preceding the assessment (35%), with 18% of participants meeting criteria for cannabis dependence in the previous year. Cannabis use, however, did not predict an increased risk of developing an acute psychosis during the follow-up period, regardless of whether cannabis use in the past year was defined as any use, frequent use, or dependent use.

Prospective Studies of Cannabis and Psychosis

The first convincing evidence that cannabis use may precipitate schizophrenia came from a 15-year prospective study of cannabis use and schizophrenia in 50 465 Swedish individuals (48). This study investigated the relation between self-reported cannabis use at age 18 years and the risk of being diagnosed with schizophrenia, as documented in the Swedish psychiatric case register, during the subsequent 15 years.

Andreasson and others found that those who tried cannabis by age 18 years were 2.4 times more likely to receive a schizophrenia diagnosis than those who had not. The risk of a schizophrenia diagnosis was related in a dose–response way to the number of times cannabis had been used by age 18 years. Compared with those who had not used cannabis, the risk of developing schizophrenia was 1.3 times higher for individuals who had used cannabis 1 to 10 times. It was 3 times higher for individuals who had used cannabis between 1 and 50 times. For individuals who had used cannabis more than 50 times, the risk of developing schizophrenia was 6 times higher, compared with those who had not used cannabis.

These risks were substantially reduced after statistical adjustment for variables related to the risk of developing schizophrenia. These included having a psychiatric diagnosis at age 18 years and having divorced parents (as an indicator of parental psychiatric disorder). Nevertheless, these relations remained statistically significant after the adjustment. Compared with individuals who never used cannabis, those who used cannabis 1 to 10 times were 1.5 times more likely to receive a schizophrenia diagnosis. Those who used cannabis 10 times or more were 2.3 times more likely to receive a schizophrenia diagnosis. Andreasson and others argued that this means that cannabis use precipitates schizophrenia in vulnerable individuals (48).

Several longitudinal studies have since supported the findings of Andreasen and others' study (Table 1). As a follow-up to the Swedish cohort study, Zammit and others reported risk over 27 years, which covers most of the risk period for the onset of psychotic disorders in a cohort that was first studied at age 18 to 20 years (49). This study improved on the earlier study in several ways: the psychiatric register provided more complete coverage of all individuals diagnosed with schizophrenia; statistical control was improved and included a larger number of potential confounding variables, such as other drug use, IQ, known risk factors for schizophrenia, and social integration; to examine the possible role of a prodrome, the study distinguished between cases that occurred in the first 5 years of the study period and those that occurred more than 5 years afterwards; and the study undertook separate analyses of individuals who only reported using cannabis at the initial assessment.

Zammit and others, as did Andreasen and others, found that cannabis use at baseline predicted an increased risk of schizophrenia during the follow-up period. They also found a dose–response relation between frequency of cannabis use at baseline and risk of schizophrenia during the follow up. They demonstrated that the relation between cannabis use and schizophrenia persisted when they statistically controlled for the effects of other drug use and other potential confounding factors, including a history of psychiatric symptoms at baseline. They estimated that 13% of schizophrenia cases could be averted if all cannabis use was prevented (that is, there was an attributable risk of 13% owing to cannabis use). The relation between cannabis use and schizophrenia was the same for the subset of the sample of individuals who only reported cannabis use at baseline, for individuals diagnosed during the first 5 years after assessment, and for individuals diagnosed during the subsequent 22 years. The relation was slightly stronger in cases observed during the first 5 years, which probably reflects the decline in cannabis use that occurs with age.

Zammit and others' findings were consistent with those of a study conducted by van Os and colleagues (50). This was a 3-year longitudinal study of the relation between self-reported cannabis use and psychosis in a community sample of 4848 individuals in The Netherlands. At baseline, subjects were assessed on cannabis and other drug use. Psychotic symptoms were assessed with a computerized diagnostic interview. Psychosis diagnoses were validated by diagnostic telephone interview with a psychiatrist or a psychologist. A consensus clinical judgment as to whether individuals had a psychotic disorder for which they needed psychiatric care was made on the basis of the interview material.

van Os and others substantially replicated the findings of the Swedish cohort and extended them in several important ways: cannabis use at baseline predicted an increased risk of psychotic symptoms during the follow-up period in individuals who did not report psychiatric symptoms at baseline; there was a dose–response relation between frequency of cannabis use at baseline and risk of psychotic symptoms during the follow-up period; those who reported any psychotic symptoms at baseline were more likely to develop schizophrenia if they used cannabis than were less vulnerable individuals ; the relation between cannabis use and psychotic symptoms persisted when van Os and others statistically controlled for the effects of other drug use; and the relation between cannabis use and psychotic symptoms was stronger for individuals with more severe psychotic symptoms who were judged to need psychiatric care. van Os and others estimated that, for individuals suffering from psychosis who were judged to need psychiatric treatment, cannabis is responsible for 13% of the risk of psychotic symptoms. They also estimated that cannabis is responsible for 50% of this risk for individuals with psychotic disorders who were judged to need psychiatric treatment.

A study by Henquet and others also replicated the Swedish and Dutch studies in a 4-year follow-up of a cohort of 2437 adolescents and young adults between 1995 and 1999 in Munich (51). At baseline, subjects were assessed by a questionnaire on cannabis use and psychotic symptoms. Psychotic symptoms were assessed, in early adulthood with the Computerized Composite International Diagnostic Interview. They found a dose–response relation between self-reported cannabis use at baseline and the likelihood of reporting psychotic symptoms. As in the Dutch cohort, young individuals who reported psychotic symptoms at baseline were much more likely to experience psychotic symptoms at follow-up if they used cannabis than were their peers who did not have such a history.

Arsenault and others reported a prospective study of the relation between adolescent cannabis use and psychosis in young adults in a New Zealand birth cohort (n = 759) whose members were assessed intensively from birth on risk factors for psychotic symptoms and disorders (52). Psychotic disorders were conservatively assessed according to DSM-IV diagnostic criteria, with corroborative reports on social adjustment from family members or friends. The researchers assessed psychotic symptoms at age 11 years, before the onset of cannabis use, and distinguished between early- and late-onset cannabis use. They also examined the specificity of the association between cannabis use and psychosis by analyzing the effects of other drug use on psychotic symptoms and disorders and of cannabis use on depressive disorders.

Arsenault and others found a relation between cannabis use by age 15 years and an increased risk of psychotic symptoms by age 26 years. Controlling for other drug use did not affect the relation. After adjusting for psychotic symptoms reported at age 11 years, the relation was no longer statistically significant, which probably reflected the small number of psychotic disorders observed in the sample. The small number of participants also limited the study's ability to examine predictors of psychotic disorders at age 26 years. The measurement of cannabis and other drug use was crude (that is, none, 1 to 2 times, and 3 or more times); however, this was more likely to work against finding relations. The specificity of the effects of cannabis on psychotic symptoms was interesting: there was no relation between other drug use and psychotic disorders, and there was no relation between cannabis use and depression. There was also an interaction between psychosis risk and age of onset of cannabis use; earlier onset was more strongly related to psychosis. Arsenault and others also suggested an interaction between cannabis use and vulnerability, with a higher risk of psychosis among cannabis users who reported psychotic symptoms at age 11 years.

Caspi and colleagues subsequently analyzed data from this cohort and reported an interaction between the risk of psychosis, cannabis use, and a functional polymorphism of the COMT gene that codes for dopamine (53). They found that the individuals in the 25% of the cohort that was homozygous for a polymorphism and used cannabis were 10.9 times more likely to develop a schizophreniform disorder than their peers with the same polymorphism who did not use cannabis. In the absence of this polymorphism, young adults who used cannabis were not at any increased risk of psychosis.

Fergusson, Horwood, and Swain-Campbell conducted a longitudinal study of the relation between cannabis dependence at age 18 years and the number of psychotic symptoms reported at age 21 years in the Christchurch birth cohort in New Zealand (54). They assessed cannabis dependence according to DSM-IV criteria and psychotic symptoms according to 10 items from the SCL-90. Because this birth cohort was assessed throughout childhood and adolescence, Fergusson and colleagues were able to adjust for a large number of potential confounding variables, including self-reported psychotic symptoms at the previous assessment, other drug use, and other psychiatric disorders. They found that cannabis dependence at age 18 years predicted an increased risk of psychotic symptoms at age 21 years (RR 2.3). This association was smaller but still significant after adjustment for potential confounders (RR 1.8). More recently, Fergusson and colleagues used a more sophisticated structural equations modelling design that accounted for both observed and nonobserved confounding factors to examine the association between cannabis use and psychotic symptoms until the individuals in this cohort were aged 25 years (55). Consistent with their earlier study, they concluded

that the association between cannabis and psychosis did not appear to be a result of confounding factors and that the association appeared to move from cannabis use to symptoms of psychosis, rather than vice versa.

The longitudinal studies find consistent associations between cannabis use in adolescence and the occurrence of psychotic symptoms in early adulthood, but all share a weakness: the temporal relation between cannabis use and the onset of psychotic symptoms is uncertain. Subjects in these studies are usually assessed once each year or less often and asked to report retrospectively on their cannabis use during the preceding number of years (often as crudely as the number of times cannabis was used or the number of times it was used weekly or monthly).

According to an experience sampling method, a French study by Verdoux and others provides greater detail on the temporal relation between cannabis use and psychotic symptoms (56). These investigators asked 79 college students to report their drug use and experience of psychotic symptoms at randomly selected time points, several times daily for 7 consecutive days. The students carried portable electronic devices through which ratings were prompted by randomly programed signals. The students comprised a stratified sample from a larger group; thus, high cannabis users ($n = 41$) and students identified as vulnerable to psychosis ($n = 16$) were overrepresented in the sample. Vulnerability to psychosis was determined during a personal interview and indicated by reporting one or more psychotic symptoms in the month prior to the study. Verdoux and others found a positive association between self-reported cannabis use and unusual perceptions; they found a negative association between cannabis use and hostility. That is, during periods of cannabis use, users reported more unusual perceptions and less hostility. These relations depended on vulnerability to psychosis: in vulnerable individuals cannabis use was more strongly associated with strange impressions and unusual perceptions, and its use did not decrease feelings of hostility as it did in individuals who lacked this vulnerability.

Self-Medication

The self-medication hypothesis is superficially plausible, but the evidence in its favour is not very compelling (8). The reasons that most individuals with schizophrenia use alcohol, cannabis, and other illicit drugs are similar to those of individuals who do not have schizophrenia: to relieve boredom, to provide stimulation, to feel good, and to socialize with peers (37,57,58). The drugs that are most often used by patients with schizophrenia are also those that are used by their peers: tobacco, alcohol, and cannabis.

In favour of the self-medication hypothesis is the evidence that some patients with schizophrenia report using cannabis because its euphoric effects relieve negative symptoms and depression (32,42,57,59). Dixon and others, for example, surveyed 83 patients with schizophrenia who reported that cannabis reduced anxiety and depression and that it increased a sense of calm, but at the cost of increased suspiciousness (42). Similar results were found in a recent Australian study (57).

The self-medication hypothesis has not typically been supported (51,55). Several prospective epidemiologic studies found that there was no relation between early psychotic symptoms and an increased risk of later cannabis use, which the self-medication hypothesis requires. The relation flowed from early cannabis use to psychosis rather than vice versa. Such negative results are supported by a study by Verdoux and others that used an experience sampling method to examine the temporal relation between cannabis use and psychotic symptoms (60). They found that there was no temporal relation between reporting unusual experiences and using cannabis, as would occur if self-medication were involved. One study of adolescents (younger than the above studies) was an exception. Ferdinand and others found an association (unadjusted for confounding variables) between early-onset psychotic symptoms and later cannabis use among this younger group (61). However, the authors did not discuss the possibility that there was an interaction between genetic vulnerabilities to psychosis and cannabis use as well as correlations between genetic vulnerabilities and cannabis use, which were purported by some commentators as possible factors to consider in the findings of the Ferdinand study (62). It is also possible that the unique changes of adolescence affected the nature of the relation between emerging psychotic symptoms and cannabis use (63). A later analysis of data from this cohort found more support for a causal role of cannabis use. Early cannabis use predicted psychotic symptoms after adjusting for preexisting psychopathology assessed by the Child Behavior Checklist (64).

Intervention Studies

If we could reduce cannabis use among patients with schizophrenia we could discover whether their disorders improved and whether their risk of relapse diminished. The major difficulty with this strategy is that it presupposes that we can successfully treat substance use disorders in individuals with schizophrenia. There are very few controlled outcome studies of substance abuse treatment in schizophrenia (65). Too few of these have produced large enough benefits of treatment or treated a large enough number of patients to provide an adequate chance of detecting any positive effects of abstinence on the course of disorders. Those that have been large enough have not reported results separately by diagnosis (66).

Biological Plausibility

THC, which acts on a specific cannabinoid receptor (CB_1) in the brain, is the principal psychoactive ingredient of cannabis (67). While historically the brain's dopaminergic system was thought to play an important role in psychotic disorders (68), there is increasing evidence that the cannabinoid system may be involved in schizophrenia and related psychotic disorders (69–72). CB_1 receptor knockout mice, for example, show behaviours consistent with some schizophrenia symptoms, such as reduced goal-directed activity and memory for temporal representations (70). Elevated levels of anandamide, an endogenous cannabinoid agonist, have also been found in the cerebrospinal fluid of individuals with schizophrenia (73). A recent case–control study found that individuals with schizophrenia had a greater density of CB_1 receptors in the prefrontal cortex, compared with control subjects (74).

A double-blind provocation study by D'Souza and colleagues showed that intravenous THC provokes positive and negative psychotic symptoms in a dose-dependent way in healthy volunteers (75). Caspi and others found a strong interaction between cannabis use and a common polymorphism in the COMT gene that suggests a biological basis for the relation that, if replicated, would explain why the risk of developing a psychosis after using cannabis is modest in the population as a whole (53).

The Role of Cannabis Potency

It is sometimes claimed that current cannabis is a different drug from that used in the 1970s and early 1980s (76). The United States is the only country that has analyzed the THC content of cannabis products over the past 3 decades. These data show an increase in THC content from 1.5% in the early 1970s, to 3.3% in the mid 1980s, and to 4.4% in 1998 (77). More recent European studies indicate that cultivars of cannabis with much higher THC are now being produced in The Netherlands (78,79), the use and effects of which will need to be investigated.

The increase in average THC content has overshadowed another important determinant of exposure to THC: a sharp decline in the age of initiation of cannabis use between 1970 and 2000 and a consequent increase in rates of regular cannabis use (80). These changes in patterns of use have increased both the amount of THC consumed and the duration of such consumption among adolescent cannabis users (76), thereby increasing their risk of dependence, poor educational performance, and psychotic symptoms.

Summary

There is currently good epidemiologic evidence from longitudinal studies in several different countries that regular cannabis use predicts an increased risk of schizophrenia and that this relation persists after controlling for confounding variables. There is very weak evidence that this relation is owing to self-medication. A contributory causal relation is also biologically plausible. Psychotic disorders involve disturbances in the dopamine neurotransmitter systems and cannabinoids, such as THC, increase dopamine release in the nucleus accumbens (81).

The evidence from prospective epidemiologic studies suggests that it is most likely that cannabis use precipitates schizophrenia in individuals who are vulnerable because of a personal or family history of schizophrenia. This hypothesis is consistent with the stress–diathesis model of schizophrenia (82,83) and evidence that a genetic vulnerability to psychosis increases the risk that cannabis users will develop psychosis (52,53,56,84). A vulnerability hypothesis is also consistent with the fact that the treated incidence of schizophrenia did not obviously increase during the 1970s and 1980s (85,86) when there were substantial increases in cannabis use among young adults in Australia and North America (38).

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[1]Senior Lecturer, National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia.
[2]Professor, School of Population Health, University of Queensland, Queensland, Australia.
Address for correspondence: L Degenhardt, National Drug and Alcohol Research Centre, University of New South Wales, Building R3, 22-32 King Street, Sydney NSW 2052 Australia; L.Degenhardt@unsw.edu.au

Résumé : L'usage du cannabis est-il une cause concourante de la psychose?

Objectif : Évaluer si l'usage du cannabis à l'adolescence et au jeune âge adulte est une cause concourante de la psychose schizophréniforme, en ce qu'il peut précipiter la psychose chez les personnes vulnérables.

Méthode : Nous avons examiné les études longitudinales d'adolescents et de jeunes adultes qui portaient sur les relations entre l'usage autodéclaré du cannabis et le risque de recevoir un diagnostic de psychose ou de déclarer des symptômes psychotiques. Nous avons aussi examiné les études qui contrôlaient d'éventuelles variables confusionnelles, comme l'usage d'autres formes de drogue et des caractéristiques personnelles qui prédisent un risque accru de psychose. Nous avons évalué les données probantes de la plausibilité biologique d'une relation causale concourante.

Résultats : Les données probantes de 6 études longitudinales menées dans 5 pays indiquent que l'usage régulier du cannabis prédit un risque accru d'un diagnostic de schizophrénie ou de déclarer des symptômes de psychose. Ces relations persistaient après le contrôle des variables confusionnelles comme les caractéristiques personnelles et l'usage d'autres drogues. La relation ne semblait pas résulter de l'usage du cannabis aux fins d'automédicamenter les symptômes de psychose. Une relation causale concourante est biologiquement plausible parce que les troubles psychotiques impliquent des perturbations des systèmes neurotransmetteurs de la dopamine, avec lesquels le système cannabinoïde interagit, comme le démontrent des études animales et une étude de provocation humaine.

Conclusion : Il est très plausible que l'usage du cannabis précipite la schizophrénie chez les personnes qui sont vulnérables, en raison d'antécédents personnels ou familiaux de schizophrénie.