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Drugs

Cannabis and psychosis

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The UK government is considering reclassifying cannabis because of concerns about links with mental health problems. What does the evidence show?

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The link between cannabis and psychosis has been extensively investigated in both epidemiological and neuroscientific studies. Epidemiological studies focus on the association between use of cannabis and development of psychosis (box), whereas neuroscientific studies have looked at how cannabis affects neurochemical functioning. However, these two lines of research have been poorly integrated, with little disciplinary cross fertilisation. We have brought together both strands of evidence to give a broader picture.

Epidemiological evidence

Contemporary interest in this topic began with a longitudinal study of Swedish conscripts reported by Andreasson and his colleagues.[1] Their findings have been replicated and extended in a series of longitudinal studies[2–6] all of which have found increased rates of psychosis or psychotic symptoms in people using cannabis (table). Furthermore, these findings of longitudinal, case-control studies have been augmented by a series of cross-sectional studies of large populations[7] and high risk populations.[8–11] These studies produce the following suggestive evidence that supports the conclusion that the link between the use of cannabis and increased risks of psychosis is likely to be causal.

Association—All studies found that the use of cannabis is associated with increased risks of psychosis or psychotic symptoms. The table shows the associations between use of cannabis and psychosis across existing longitudinal studies; odds ratios range from 1.77 to 10.9, with a median of 2.23-2.3.

Dose response—Although most studies have compared cannabis users and non-users, several studies have shown that the increasing use of cannabis is

What is psychosis?

Psychosis is used in this research as a generic description of severe mental illness characterised by the presence of delusions, hallucinations, and other associated cognitive and behavioural impairments that interfere with the ability to meet the ordinary demands of life.

It is measured either by using standardised diagnostic criteria for psychotic conditions such as schizophrenia or by using validated scales that rank the level of psychotic symptoms from none to severe.

PHILLIPPE HAYS/REX

Demonstrator for the legalisation of cannabis

Summary of prospective studies of cannabis use and psychotic symptoms

Study	Sample	Assessment	Outcome measure	Adjusted association between cannabis and psychosis* (95% CI)
Andreasson et al[1]	45 570 male Swedish military conscripts aged 18- 21	At 15 year follow-up	Clinical diagnosis of schizophrenia	Highest level of use: Relative risk 2.3 (1.0 to 5.3)
Arsenault et al[2]	759 members of New Zealand birth cohort	At age 26	DSM-IV criteria for schizophreniform disorder	Cannabis users by age 15: Odds ratio 1.95 (0.76 to 5.01)
Caspi et al[3]	803 members of New Zealand birth cohort	At age 26	DSM-IV criteria for schizophreniform disorder	Participants with Val/Val variant of COMT gene: Odds ratio 10.9 (2.2 to 54.1)
Fergusson et al[4]	1055 members of New Zealand birth cohort	At age 25	No of psychotic symptoms in past month†	Daily cannabis users: Incident rate ratio=1.77 (1.28 to 2.44)
Henquet et al[5]	2437 German participants aged 14 to 24	At baseline and four year follow up	At least one "broad" or two "narrow" psychosis outcomes‡	Daily cannabis users: Odds ratio 2.23 (1.30 to 3.84)
van Os et al[6]	4104 participants in Dutch general population study	Assessed three times over four years	≥1 positive rating on psychotic symptom items§	Highest level of use: Odds ratio 6.81 (1.79 to 25.92)

DSM-IV= *Diagnostic and statistical manual of mental disorders*, fourth edition.
*Compared with non-users.
†Scored on 10 items from symptom checklist (SCL-90).
‡Composite international diagnostic interview (Munich version).
§Brief psychiatric rating scale.

associated with an increasing risk of psychosis,[1 4 6] with odds ratios or relative risk for the groups with highest use groups increasing to 6.0,[1] 1.77,[4] and 6.81.[6]

Assessment of outcome—The associations between cannabis use and psychotic symptoms have proved robust to different methods of assessing outcomes. Associations have been found using various outcome measures including clinical diagnoses of psychoses,[1] diagnostic classifications based on self report data,[2 3] and symptom scores.[2–6]

Confounding—The validity of studies of cannabis is threatened by the possibility of residual uncontrolled confounding factors. More recent studies[2–6] have controlled for a wide range of factors that could confound the relation between cannabis and psychosis—for example, genotype, sex, age, psychosis before using cannabis, education, personality, IQ, affiliation with deviant peers, conduct and attention disorders, other substance use, social functioning, previous mental health, parental age, parental divorce, changes in parents, parental attachment, parental offending and substance use, socioeconomic factors, physical and sexual abuse, and childhood trauma.

Reverse causality—A further threat to the validity of claims of a link between cannabis and psychosis comes from the possibility of a reverse causal association in which the development of psychotic symptoms encourages the use of cannabis, perhaps as self treatment. To control for reverse causality, prospective studies have assessed the use of cannabis before the onset of psychotic symptoms.[2–6] In addition, a recent study used structural equation modelling to examine the causal linkages between cannabis and psychotic symptoms.[4] This study concluded that although use of cannabis was associated with increased rates of psychotic symptoms, the development of psychotic symptoms was associated with a decrease in rates of use of cannabis.

Effect modification—Further evidence suggests that use of cannabis is linked with development of psychotic symptoms in people who are susceptible to developing psychotic symptoms, including those with a past diagnosis of a psychotic disorder,[6] those reporting psychotic or paranoid symptoms at baseline,[5] and those with a family history of psychotic disorder.[8] A recent behavioural genetic study found that this link is stronger in those who have the Val/Val variant of the catechol-O-methyltransferase (COMT) gene.[3] This gene has a role in regulating dopamine concentrations and has been implicated in the development of schizophrenia (see below).

In summary, epidemiological research using longitudinal designs has produced suggestive evidence of a causal link between the use of cannabis and the development of psychosis or psychotic symptoms. This link has been shown to be robust and resilient; however, questions may still be raised regarding the measurement of psychotic symptoms, control for confounding factors, and the possibility of reverse causality. Priorities for future research include improving techniques for covariate control, and assessing the precise nature of the symptoms or disorders that may be associated with cannabis use.

Pathways to psychosis and psychotic symptoms

The psychotropic effects of cannabis are due largely to the effects of Δ^9-tetrahydrocannabinol on specific cannabinoid receptors in the brain.[12] Three receptor types (CB1-CB3) have been identified, with CB1 being the most common in the brain and having particularly high densities in the neocortex, limbic system, and basal ganglia.[12 13] The CB1 and CB3 receptors both regulate the release of several key neurotransmitters in the brain, including γ-aminobutyric acid (GABA), glutamate, dopamine, noradrenaline, serotonin, and acetylcholine.[13] Therefore, the use of cannabis may set in train a cascade of changes in neurotransmitter functioning. The precise effects of these chemical changes on brain function are difficult to predict since they will depend on the time course of the diffusion of Δ^9-tetrahydrocannabinol and which specific cannabinoid receptors are activated.[12 13]

Despite the complexities of the effects of Δ9-tetrahydrocannabinol on the brain, evidence from both animal and human studies suggests that it has short term effects on behavioural and cognitive functioning.[14] In animals, these effects include a potentiation of the stereotyped behaviour caused by amphetamines, which many researchers believe is linked to psychotic behaviour in humans.[14] In a study of the acute effects of Δ9-tetrahydrocannabinol in humans, D'Souza and colleagues observed both

positive and negative schizophrenic-like responses using the positive and negative symptom scale.[15] However, these responses are not permanent and seem to reflect the transient effects of Δ9-tetrahydrocannabinol on behavioural and cognitive functioning.[16] Nevertheless, repeated Δ9-tetrahydrocannabinol exposure in susceptible people may lead to permanent changes in neurotransmitter functioning that could then lead to the development of longer term tendencies to psychotic illness.

The neurological pathways that link cannabis use and increased psychotic symptoms are not entirely clear. The most likely pathways involve the effects of Δ9-tetrahydrocannabinol on the regulation of dopamine and serotonin within the brain. Both of these neurotransmitters are known to have a role in maintaining the psychotic state.[17] The dopamine hypothesis of schizophrenia proposes that psychotic symptoms are caused, at least in part, by an increase in dopamine neurotransmission by nerve fibres that project into the limbic system and neocortex.[17] Firm evidence shows that, depending on the site in the brain, the stimulation of cannabinoid receptors by Δ9-tetrahydrocannabinol may either inhibit or increase the release of dopamine.[18–21] Cheer and colleagues have shown that drugs that activate CB1 receptors increase dopamine release in the limbic system.[21]

The view that dopamine effects are one pathway by which cannabis may lead to psychosis is supported by behavioural genetic research which has shown that people with the Val/Val variant of the COMT gene have a greater susceptibility to cannabis-induced psychosis.[3] The COMT gene is believed to be important in regulating the metabolism of dopamine. The finding that a gene that regulates dopamine activity modifies the responsiveness to cannabis adds credence to the hypothesis that the effect of cannabis on dopamine release is one mechanism by which cannabis use may increase the risks of psychosis and psychotic symptoms.

In summary, neuroscientific studies of the effects of cannabis on neurological functioning have produced both firm and suggestive evidence that cannabis affects the dopamine system, which is known to have a key role in the development of psychotic symptoms. At present, the precise pathways by which these effects occur is unclear, but the more general observation of the dopaminergic effects of cannabis is well established.

Does cannabis cause psychosis?

The issue of whether cannabis leads to increased risks of psychosis and psychotic symptoms is likely to remain contentious given the uncertainties that exist in both the epidemiological and neuroscientific evidence. Within epidemiology, the evidence for a causal link is suggestive, but issues relating to measurement, confounding, and reverse causality are likely to remain causes for concern. On the other hand, although the current neuroscientific research is still a long way from definitive conclusions about how regular use of cannabis could lead to the development of psychoses, the evidence to date has been firm.

Summary points

Epidemiological evidence suggests a persistent association between cannabis use and psychosis that is robust to methodological challenges

Neuroscientific studies show that cannabis may lead to psychosis through effects on the processing of dopamine in the brain

Taken together, this evidence suggests a causal relation in which frequent use of cannabis leads to a greater risk of psychotic symptoms

The implications for policy and the legal status of cannabis are unclear as most people who use cannabis do not develop psychotic symptoms

We can approach evidence containing uncertainty in two ways. The first is to argue that the presence of uncertainty precludes any firm conclusions from being drawn. However, this approach tends to discount what is known about the relation between cannabis and mental health on the grounds that there may be non-observed and unknown factors that explain the association and fails to recognise that all scientific evidence contains sources of uncertainty. Relentless application of this logic will lead to the conclusion that nothing can be known about anything because of real or imagined flaws in the evidence.

The alternative approach is to draw interim conclusions based on the weight of the available evidence but to acknowledge the uncertainties within that evidence. This approach provides a more accurate summary of the evidence and avoids the difficulties of the first approach. Thus, it is reasonable to conclude that the weight of the epidemiological and neuroscientific evidence supports the conclusion that the use (particularly frequent use) of cannabis may alter brain functioning in susceptible individuals leading to increased risks of psychosis and psychotic symptoms. These conclusions are tempered by uncertainties arising from the correlational nature of epidemiological studies of cannabis and psychosis; and the lack of evidence about the specific pathways by which cannabis may affect brain function.

Finally, these conclusions raise important issues about both the public health and legal responses to cannabis use. For example, recent changes to cannabis laws in the UK, and a review of these changes, have been informed at least in part by scientific research on the effects of cannabis use, including some of the studies cited here.[22] Research findings such as these are often used in a simplistic manner to support both positions for and against cannabis in legal and policy debates. However, the implications are more complex and subtle. Although the regular use of cannabis may increase risks of psychotic symptoms, most of those who use cannabis regularly do not develop psychosis and most cases of psychosis are not attributable to cannabis.

Estimates of the population attributable risk suggest that the use of cannabis accounts for about

10% of cases of psychosis.[2 6] The task of deciding the harms of cannabis involves what Hall and Pacula[23] have described as a "choice of evils" in which the rights of the majority who use cannabis without experiencing problems are balanced against the risks of a minority who may develop serious health consequences. The implications of these findings for both public health policy on cannabis, and the legal status of cannabis, are by no means straightforward or self evident. We need to develop an informed consensus on the risks posed by cannabis and the mechanisms for dealing with such risks.

Contributors and sources: DMF and RP are directors of the Christchurch Health and Development Study and the Dunedin Multidisciplinary Health and Development Study, respectively, and each has published extensively on the epidemiology of cannabis use. PFS is an expert on pharmacology and the neurological effects of cannabis use. JMB has published articles on the epidemiology of cannabis use and other substance use as a member of the Christchurch Health and Development Study. The article is based on a literature search through Pubmed. DMF had the idea for the article and PFS and JMB did the literature search. All authors contributed to writing the article. DMF is guarantor.

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Science commentary: Cannabis confusions

Geoff Watts

Debates about cannabis are not confined to its value as a medicine or to its possible hazards as a recreational drug.[1] Something much more fundamental has been engaging the experts for years: its taxonomy. Are all plants belonging to the genus *Cannabis* mere varieties of a single species—or is it correct to recognise at least three separate species?

In his original 1753 classification, Carl Linnaeus identified just one, *Cannabis sativa*. The first indication of dissent came in 1785 when another eminent biologist, Jean-Baptiste Lamarck, was given some plant specimens collected in India. On the basis of several characteristics including their firm stems, thin bark, and the shape of their leaves and flowers, Lamarck felt that they should be distinguished from *C sativa*. Accordingly he invoked a new species, *C indica*.

In a lengthy and detailed review of the cannabis species problem, Ernest Small of the Canadian Biosystematics Research Institute commented that Lamarck seems to have reached his decision after "relatively little study."[2] He adds that "in the 'exploratory age' of plant taxonomy scientists often were forced to come to conclusions on the basis of very limited material."

The third and least well founded species is *C ruderalis*. This was the name that a Russian, Janischevsky, gave to the cannabis plants he found growing in the south eastern central region of his country. The differences he noted were mostly in the size, shape, and casing of the seeds. And even Janischevsky himself seems not to have been totally convinced that these justified a new species.

Debates among "splitters" and "lumpers" over the correct classification of *Cannabis* rumbled on for much of the last century, although the lumpers seem to have won the majority vote. One commonly expressed opinion is that *indica*, *ruderalis*, and other so-called species should be regarded as no more than sub-species or even variants of *C sativa*.[3]

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