Cannabis use and psychotic disorders: an update

WAYNE HALL¹, LOUISA DEGENHARDT² & MAREE TEESSON²

¹Office of Public Policy and Ethics, Institute for Molecular Bioscience, University of Queensland, Australia and ²National Drug and Alcohol Research Centre, University of New South Wales, Australia

Abstract

This paper evaluates three hypotheses about the relationship between cannabis use and psychosis in the light of recent evidence from prospective epidemiological studies. These are that: (1) cannabis use causes a psychotic disorder that would not have occurred in the absence of cannabis use; (2) that cannabis use may precipitate schizophrenia or exacerbate its symptoms; and (3) that cannabis use may exacerbate the symptoms of psychosis. There is limited support for the first hypothesis. As a consequence of recent prospective studies, there is now stronger support for the second hypothesis. Four recent prospective studies in three countries have found relationships between the frequency with which cannabis had been used and the risk of receiving a diagnosis of schizophrenia or of reporting psychotic symptoms. These relationships are stronger in people with a history of psychotic symptoms and they have persisted after adjustment for potentially confounding variables. The absence of any change in the incidence of schizophrenia during the three decades in which cannabis use in Australia has increased makes it unlikely that cannabis use can produce psychoses that would not have occurred in its absence. It seems more likely that cannabis use can precipitate schizophrenia in vulnerable individuals. There is also reasonable evidence for the third hypothesis that cannabis use exacerbates psychosis. [Hall W, Degenhardt L, Teesson M. Cannabis use and psychotic disorders: an update. Drug Alcohol Rev 2004;23:433 – 443]

Key words: cannabis, psychosis.

Introduction

There is abundant epidemiological evidence of an association between cannabis use and psychotic symptoms and disorders (e.g. [1,2]) but the reasons for the association have been controversial. Thornicroft [3] examined the evidence supporting an association between cannabis and psychosis but was unable to draw strong conclusions about causality. Nearly a decade later, Hall [1] came to a similar conclusion. Both authors argued that prospective longitudinal population-based cohort studies were required to elucidate any causal role that cannabis use may play in psychosis. We reconsider the question in the light of four prospective epidemiological studies that have recently been published.

The nature of any relationship between cannabis use and psychosis remains an important issue. Cannabis has been used by most young Australians in late adolescence and early adulthood, the peak risk period for the onset of psychoses. These disorders can be disabling and they carry an elevated risk of premature death by suicide [4]. The continuing debate about the legal status of recreational cannabis in Australia and other developed societies ensures that the evidence on this issue carries special policy weight. It is accordingly important to review the evidence carefully and critically but without setting standards for proof unreasonably high and thereby precluding sensible policy recommendations.

Possible types of relationship between cannabis use and psychoses

It is useful to begin by distinguishing three possible types of hypotheses about relationships between cannabis use and psychosis [1]. The strongest hypothesis is that heavy cannabis use causes a unique ‘cannabis psychosis’. This hypothesis assumes (a) that the psychosis would not occur in the absence of cannabis use, and (b) that the causal role of cannabis can be inferred from the type of psychotic symptoms reported,
and the fact that these symptoms are preceded by heavy cannabis use and remit swiftly after abstinence from cannabis.

A second hypothesis is that cannabis use may precipitate an episode of schizophrenia. This hypothesis assumes that cannabis use is one factor among many others (including genetic predisposition and other unknown causes) that may act together to precipitate schizophrenia. It does not assume that a causal role for cannabis can be inferred from the symptoms of the disorder, or that the disorder will necessarily remit when cannabis use ceases. It does not assume that cannabis use is either a necessary or a sufficient cause of schizophrenia.

Thirdly, cannabis use may exacerbate the symptoms of schizophrenia. If cannabis use can precipitate schizophrenia, it is also likely to exacerbate its symptoms. However, cannabis use may exacerbate symptoms of schizophrenia (even if it is not a precipitant of the disorder) by reducing compliance with treatment, or interfering with the effects of the neuroleptic drugs that are used to treat it.

Making causal inferences

In order to infer that cannabis use is a cause of psychosis in any of these ways we need evidence that there is an association between cannabis use and psychosis; that cannabis use preceded the psychosis; and that plausible alternative explanations of the association can be excluded [5].

Association requires that cannabis use and psychosis occur together. This means that cannabis users should have higher rates of psychosis and that cannabis use should occur more frequently among people with psychoses. As indicated above, the fact of an association is not in doubt; it is its interpretation that is contested. Associations between cannabis use and psychosis may occur because psychosis leads to cannabis use. To rule out this possibility, cannabis use needs to be shown to precede the onset of psychosis. An association between cannabis use and psychosis also has to be shown to arise from cannabis use and not from some uncontrolled factors that are associated with cannabis use and psychosis (such as for example other drug use, or a genetic predisposition to develop schizophrenia and use cannabis).

We first review the evidence for the strongest causal hypothesis, that heavy cannabis use causes a unique ‘cannabis psychosis’.

A ‘cannabis psychosis’

There are case reports of ‘cannabis psychoses’ [6–9] that describe individuals who develop psychotic disorders after using cannabis. Chopra & Smith [7] reported one of the largest, a series of 200 patients who were admitted to a psychiatric hospital in Calcutta between 1963 and 1968 with psychotic symptoms that followed the use of cannabis. The most common symptoms ‘were sudden onset of confusion, generally associated with delusions, hallucinations (usually visual) and emotional lability... amnesia, disorientation, depersonalisation and paranoid symptoms’ (p. 24). Most psychoses were preceded by using large amounts of cannabis and those who used the most potent cannabis developed psychoses after the shortest periods of use.

The findings of Chopra & Smith have been supported by case series which suggest that large doses of potent cannabis products can produce a ‘toxic’ psychotic disorder with ‘organic’ features of amnesia and confusion. These disorders have been reported in the Caribbean [10], New Zealand [11], Scotland [9], South Africa [8], Sweden [6] and the United Kingdom [12].

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 had no personal or family history of psychosis; their symptoms remitted within days to weeks of enforced abstinence from cannabis use; recovery was complete, with the person having no residual psychotic symptoms such as those seen in schizophrenia; and if the disorder recurred, it was only after the individual resumed cannabis use [1].

Some commentators [3,13] have criticized the poor information on cannabis use and its relationship to the onset of psychosis, the person’s premorbid adjustment and their family history of psychosis. They also emphasize the varied clinical picture of ‘cannabis psychoses’ as reported by different observers.

A number of controlled studies have been conducted over the past 20 years [14–19]. Studies have either compared people with ‘cannabis psychoses’ with people who have schizophrenia, or compared psychoses occurring in people who have and have not used cannabis prior to presenting for treatment. Their results have been mixed, in part because of the small sample sizes and variations in research methods [1].

Summary

The evidence for there being a distinct ‘cannabis psychosis’ is weak. The lack of support for ‘a cannabis psychosis’ does not, however, rule out the hypothesis that cannabis use may precipitate an episode of schizophrenia. The evidence for this is reviewed below.
Association between cannabis use and psychosis

Several studies have examined the relationship between cannabis use and psychotic symptoms in the general population. Tien & Anthony [20] used data from the Epidemiologic Catchment Area study to examine correlates of reporting one or more ‘psychotic experiences’ (four types of hallucinations and seven types of delusional belief). They compared 477 cases who reported one or more of these symptoms in a 1-year follow-up with 1818 controls who did not. Cases and controls were matched for age and social and demographic characteristics. Daily cannabis use was found to double the risk of reporting psychotic symptoms (after statistical adjustment for alcohol use and psychiatric diagnoses at baseline).

Thomas [21] reported the prevalence of psychotic symptoms among cannabis users in a random sample of people drawn from the electoral role of a large city in the North Island of New Zealand. One in seven (14%) cannabis users reported ‘strange, unpleasant experiences such as hearing voices or becoming convinced that someone is trying to harm you or that you are being persecuted’ after using cannabis.

The National Survey of Mental Health and Well-being (NSMHWB) conducted in Australia in 1997 included a screening questionnaire for psychotic symptoms [1]. Among those under 50 years of age who screened positive for a psychotic disorder, 7.8% (n = 27) met International Classification of Diseases (ICD)-10 criteria for cannabis dependence in the past 12 months. This was 17.2% of all persons diagnosed with cannabis dependence. A diagnosis of cannabis dependence increased the chances of reporting psychotic symptoms 1.71 times, after adjusting for age, affective and anxiety disorders, smoking status and alcohol dependence [2].

Association between schizophrenia and cannabis use

In case–control studies [22,23], patients with schizophrenia are more likely to use cannabis than other psychiatric patients or normal controls [24]. The prevalence of use in schizophrenia patients has varied between studies but it is generally higher than rates in the general population [24]. These variations are probably due to differences in the sampling of patients, with younger cases reporting higher rates than older people with chronic disorders. Generally, cannabis is the most commonly used drug after alcohol and tobacco, and it is often used with alcohol [25,26].

The controlled clinical studies provide conflicting evidence on the correlates of substance abuse in schizophrenia, apart from the consistent finding that young males are over-represented among cannabis users [1], as they are in the general community [27]. In some studies, cannabis users have had an earlier onset of psychotic symptoms, a better premorbid adjustment, more episodes of illness and more hallucinations [26,28,29]. Other controlled studies have failed to replicate some of these findings [30–32].

A recent clinical study has adopted a novel approach to studying the relationship between cannabis use and psychosis [33]. In this study, 100 young people (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 of the following: 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 assessment (35%), with 18% 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 was defined as any use, frequent use or dependent use in the past year. The rate of cannabis use was low by comparison with the other studies and this, in combination with the small number of cases, may explain the absence of an association.

Community surveys of psychiatric disorders, such as the ECA, have also reported higher rates of substance use disorders among persons with schizophrenia [34]. Nearly half the patients identified as having schizophrenia in the ECA study had a diagnosis of substance abuse or dependence (34% for an alcohol disorder and 28% for another drug disorder) [35]. These rates were higher than the rates in general population, namely, 14% for alcohol disorders [36] and 6% for drug abuse [34]. The most common patterns of substance use among 231 cases of schizophrenia in the ECA study were: alcohol (37%) and cannabis (23%), followed by stimulants and hallucinogens (13%), narcotics (10%) and sedatives (8%). The most common combination of drugs was alcohol and cannabis use (31%) [31]. These findings were replicated in Edmonton, Alberta [37].

In the Australian NSMHWB, 11.5% of those who reported that they had been diagnosed with schizophrenia, met ICD-10 criteria for a cannabis use disorder in the past 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.

The important questions in explaining the elevated rates of cannabis use among people with schizophrenia are: does cannabis use usually precede psychosis? Can we rule out the possibility of other causes that may explain the association? The best evidence for answering these questions comes from longitudinal popula-
tion-based studies that have assessed cannabis use before the onset of psychotic symptoms, followed the cohort over a substantial period and used statistical methods to assess the contribution of factors other than cannabis use.

**Explanations of the association**

One explanation of the association is that cannabis use precipitates schizophrenia in vulnerable people. This is consistent with the earlier age of onset of psychosis among cannabis users (with their drug use typically preceding symptoms), and the fact that cannabis users who develop schizophrenia often have better premorbid adjustment, fewer negative symptoms and better treatment outcome [38].

Another possibility is that the association between cannabis use and an early onset and good prognosis are spurious. Arndt et al. [29] argue that individuals with schizophrenia with a better premorbid personality are more likely to be offered cannabis by peers than people with schizophrenia who are socially withdrawn. There is also evidence [39] that people with acute onset psychoses usually have a better premorbid adjustment and a better prognosis. They also have greater opportunities to use cannabis and other illicit drugs than especially withdrawn people whose illness has an insidious onset.

A third possibility is that cannabis use is a consequence (rather than a cause) of schizophrenia. For example, cannabis and other drugs may be used to medicate the unpleasant symptoms of schizophrenia, such as, depression, anxiety, lethargy and anhedonia, or the unpleasant side effects of the neuroleptic drugs that are often used to treat the disorder [29].

**The Swedish conscript study**

Until very recently, the most convincing evidence that cannabis use precipitates schizophrenia came from a 15-year prospective study of cannabis use and schizophrenia in 50 465 Swedish conscripts [40]. This study investigated the relationship between self-reported cannabis use at age 18 and the risk of being diagnosed with schizophrenia in the Swedish psychiatric case register during the next 15 years.

Andreasson et al. [40] found that those who had tried cannabis by age 18 were 2.4 times more likely to receive a diagnosis of schizophrenia than those who had not. The risk of a diagnosis of schizophrenia was related to cannabis use in a dose–response manner to the number of times cannabis had been used by age 18. Compared with those who had not used cannabis, the risk of developing schizophrenia was 1.3 times higher for those who had used cannabis one to 10 times, three times higher for those who had used cannabis between one and 50 times, and six times higher for those who had used cannabis more than 50 times.

These risks were reduced substantially after statistical adjustment for variables that were related to the risk of developing schizophrenia. These included having a psychiatric diagnosis at age 18, and having parents who had divorced (as an indicator of parental psychiatric disorder). Nevertheless, these relationships remained statistically significant after adjustment. Compared with those who had never used cannabis, the those who had used cannabis one to 10 times were 1.5 times more likely, and those who had used 10 or more times were 2.3 times more likely to receive a diagnosis of schizophrenia. Andreasson et al. [40] argued that this means that cannabis use precipitates schizophrenia in vulnerable individuals.

Other authors offered a number of alternative explanations of the Swedish finding. First, there was a large temporal gap between self-reported cannabis use at age 18 and the development of schizophrenia over the next 15 years or so [41]. The diagnosis of schizophrenia was based upon a case register, so there was no data on how many individuals used cannabis up until the time that their schizophrenia was diagnosed. Andreasson et al. argued that cannabis use persisted because cannabis use at age 18 was also related strongly to the risk of attracting a diagnosis of drug abuse.

A second possibility was that schizophrenia had been misdiagnosed. On this hypothesis, the higher rate of ‘schizophrenia’ among heavy cannabis users reflected cannabis-induced psychoses which were diagnosed mistakenly as schizophrenia [41]. Andreasson et al. [40] examined 21 cases of schizophrenia among conscripts in the case register (eight of whom had used cannabis and 13 of whom had not). They found that 80% of these cases met the DSM-III requirement that the symptoms had been present for at least 6 months, thereby excluding the diagnoses of transient drug-induced psychotic symptoms.

A third hypothesis was that the relationship between cannabis use and schizophrenia was due to the use of amphetamines. People who use cannabis in adolescence are at higher risk of later using amphetamines [42], which can produce an acute paranoid psychosis [43]. Amphetamines were the major illicit drugs of abuse in Sweden during the study period [44]. The evidence that psychotic symptoms persisted beyond 6 months [40] also makes this an unlikely hypothesis.

A fourth hypothesis was that cannabis use at age 18 was a symptom of emerging schizophrenia. Andreasson et al. [40] rejected this hypothesis, noting that the cannabis users who developed schizophrenia had better premorbid personalities, a more abrupt onset and more positive symptoms than the non-users who developed schizophrenia. Moreover, there was still a dose–response relationship between cannabis use and schizo-
philosophy among those who had no history of psychiatric disorder. The persuasiveness of this evidence depends upon how confident we can be that a failure to identify a psychiatric disorder at conscription meant that no disorder was present.

A fifth hypothesis depended upon the validity of the self-reported cannabis use at conscription. Andreasen et al. [40] acknowledged that cannabis use was probably under-reported because this information was not collected anonymously. They argued, however, that this would underestimate the relationship between cannabis use and schizophrenia. This is true if the schizophrenia and non-schizophrenia conscripts were equally likely to under-report. If, for example, pre-schizophrenia subjects were more candid about their drug use, then the apparent relationship between cannabis use and schizophrenia could be due to response bias [41]. This seems unlikely in view of the strong dose–response relationship between the frequency of cannabis use by age 18, and the large unadjusted relative risk of schizophrenia among heavy users.

Zammit et al. [45] has recently reported a follow-up of the Swedish cohort study, reporting on risk over a 27-year follow-up that covers most of the risk period for the onset of psychotic disorders in a cohort that was first studied when 18–20 years old. This study improved on the earlier study in a number of ways. The psychiatric register provided more complete coverage of all cases diagnosed with schizophrenia; there was better statistical control of a larger number of potential confounding variables, including other drug use, IQ, known risk factors for schizophrenia and social integration; 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 in order to look at the possible role of a prodrome; and the study undertook a separate analyses in those who only reported using cannabis at the initial assessment.

Zammit et al. [45] found, as did Andreasen et al. [40], that cannabis use at baseline predicted an increased risk of schizophrenia during the follow-up period. They also found a dose–response relationship between frequency of cannabis use at baseline and risk of schizophrenia during the follow-up. They demonstrated that the relationship between cannabis use and schizophrenia persisted when they controlled statistically 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 cases of schizophrenia could be averted if all cannabis use were prevented (i.e. the attributable risk of cannabis to schizophrenia was 13%). The same relationships were observed in the subset of the sample who reported cannabis use only at baseline and among cases diagnosed in the first 5 years after assessment and for the 22 years afterwards. The relationship was a little stronger in cases observed in the first 5 years, probably reflecting the decline in cannabis use that occurs with age.

The NEMESIS study

Zammit et al.’s [45] findings have been supported by a study conducted by Van Os and colleagues [46]. This was a 3-year longitudinal study of the relationship between self-reported cannabis use and psychosis in a community sample of 4848 people in the Netherlands. Subjects were assessed at baseline on cannabis and other drug use. Psychotic symptoms were assessed using a computerized diagnostic interview. A diagnosis of psychosis was validated in positive cases by a diagnostic telephone interview with a psychiatrist or psychologist. A consensus clinical judgement was made on the basis of the interview material as to whether individuals had a psychotic disorder for which they were in need of psychiatric care.

Van Os et al. [46] substantially replicated the findings of the Swedish cohort and extended them in a number of important ways. First, cannabis use at baseline predicted an increased risk of psychotic symptoms during the follow-up period in individuals who had not reported psychiatric symptoms at baseline. Secondly, there was a dose–response relationship between frequency of cannabis use at baseline and risk of psychotic symptoms during the follow up period. Thirdly, the relationship between cannabis use and psychotic symptoms persisted when they controlled statistically for the effects of other drug use. Fourthly, the relationship between cannabis use and psychotic symptoms was stronger for cases with more severe psychotic symptoms that were adjudged to need psychiatric care. Van Os et al. [46] estimated the attributable risk of cannabis to psychosis was 13% for psychotic symptoms and 50% for cases with psychotic disorders adjudged to need psychiatric treatment. Fifthly, those 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. They estimated that cannabis use accounted for 80% of the increased risk of developing a psychotic disorder that warranted treatment among vulnerable individuals.

The Dunedin study

Arsenault et al. [47] reported a prospective study of the relationship between adolescent cannabis use and psychosis in young adults in a New Zealand birth cohort (n = 759) whose members had been assessed intensively on risk factors for psychotic symptoms and disorders since birth. Psychotic disorders were assessed
conservatively according to DSM-IV diagnostic criteria, with corroborative reports from family members or friends on social adjustment. They assessed psychotic symptoms at age 11 before the onset of cannabis use and distinguished between early and late onset of cannabis use. They also examined the specificity of the association between cannabis use and psychosis by conducting analyses of the effects of: (i) other drug use on psychotic symptoms and disorders; and (ii) cannabis use on depressive disorders.

Arsenault et al. [47] found a relationship between cannabis use by age 15 and an increased risk of psychotic symptoms by age 26. The relationship did not change when they controlled for other drug use, but it was no longer statistically significant after adjustment for reporting psychotic symptoms at age 11. The latter probably reflected the small number of psychotic disorders observed in the sample. The small number of cases also limited the ability of the study to examine predictors of psychotic disorders at age 26. The measurement of cannabis and other drug use was crude (namely: none, one, two or three or more times) although this was more likely to work against finding relationships. An interesting result was the specificity of the effects of cannabis on psychotic symptoms: there was no relationship between other drug use and psychotic disorders and no relationship between cannabis use and depression. There was also an interaction between psychosis risk and age of onset of cannabis use, with earlier onset being more strongly related to psychosis. There was also the suggestion of an interaction between cannabis use and vulnerability, with a higher risk of psychosis among cannabis users who reported psychotic symptoms at age 11.

The Christchurch Health and Development study

Fergusson, Horwood & Swain-Campbell [48] have reported a longitudinal study of the relationship between cannabis dependence at age 18 and the number of psychotic symptoms reported at age 21 in the Christchurch birth cohort in New Zealand. They assessed cannabis dependence using DSM-IV criteria, and psychotic symptoms were assessed by 10 items from the SCL-90. Because this was a birth cohort that had been assessed throughout childhood and adolescence, Fergusson et al. 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 predicted an increased risk of psychotic symptoms at age 21 years [relative risk (RR) of 2.3]. This association was smaller but still significant after adjustment for potential confounders (RR of 1.8).

Limitations of the longitudinal studies

The longitudinal studies find consistent associations between cannabis use in adolescence and the occurrence of psychotic symptoms in early adult life but all share a weakness: there is uncertainty about the temporal relationship between cannabis use and the timing of the onset of psychotic symptoms. Subjects in these studies have usually been assessed once a year or less often, and asked to report retrospectively on their cannabis use during the preceding number of years. Moreover, cannabis use has often been crudely assessed by the number of times that cannabis was used or the number of times it was used per week or month.

A recent French study improves upon these limitations by providing greater detail on the temporal relationship between cannabis use and psychotic symptoms by using an experience sampling method to study the relationship [49]. These investigators asked 79 college students to report on their drug use and experience of psychotic symptoms at randomly selected time-points, several times each day over 7 consecutive days. The ratings were prompted by randomly programmed signals sent to a portable electronic device that the students carried. The students were a stratified sample from a larger group in which high cannabis users (n = 41) and students identified as vulnerable to psychosis (n = 16) were over-represented. Vulnerability to psychosis was indicated by reporting one or more psychotic symptoms in the past month during a personal interview.

Verdoux et al. [49] found a positive association between self-reported cannabis use and unusual perceptions and a negative association between cannabis use and hostility. That is, in time-periods when cannabis was used, users reported more unusual perceptions and less hostility. These relationships depended upon 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 in the way that it did in individuals who lacked this vulnerability. They also found a relationship between self-reported use of psychostimulant drugs and unusual perceptions and thought influence but these relationships were independent of those between cannabis use and psychotic experiences. There was no temporal relationship between reporting unusual experiences and using cannabis use, as would be expected if some form of self-medication were involved.

Exacerbation of schizophrenia

The final relationship examined in this paper is whether cannabis use exacerbates the symptoms of schizophrenia. Clinical reports clearly suggest that patients with
schizophrenia who continue to use cannabis have more psychotic symptoms [50], respond poorly to neuroleptic drugs [51] and have a worse clinical course than those patients who do not [52]. These reports have been supported by a small number of controlled studies.

Negrete et al. [53] conducted a retrospective study of the relationship between self-reported cannabis use and symptoms using clinical records in 137 schizophrenic patients who had a disorder for at least 6 months. They compared the rates of hallucinations, delusions and hospitalizations among cannabis users with those among patients who had previously used cannabis and those who had never used cannabis. There were higher rates of hallucinations, delusions and more hospitalizations among current cannabis users, and these relationships persisted after statistical adjustment for age and sex differences between the groups.

Cleghorn et al. [54] compared the symptom profiles of schizophrenic patients with histories of substance abuse, among whom cannabis was the most heavily used drug. Drug users had a higher prevalence of hallucinations, delusions and positive symptoms than those who did not use drugs.

Jablensky et al. [55] reported a 2-year follow-up of 1202 first-episode schizophrenic patients in a 10-country WHO Collaborative study. They found that the use of ‘street drugs’, including cannabis and cocaine, during the follow-up period predicted more psychotic symptoms and hospitalization. Martinez-Arvalo et al. [56] also reported that continued use of cannabis during a 1-year follow-up of 62 DSM-diagnosed schizophrenia patients predicted a higher rate of relapse and poorer compliance with anti-psychotic drug treatment.

Linszen et al. [57] reported a prospective study of 93 psychotic patients whose symptoms were assessed monthly over a year. Twenty-four of their patients were cannabis users (11 were less than daily users and 13 were daily cannabis users). Despite the small samples, they found that the cannabis users relapsed to psychotic symptoms sooner, and had more frequent relapses in the year of follow-up, than the patients who had not used cannabis. There was also a dose–response relationship: daily users relapsed earlier and more often than the less than daily users who, in turn, relapsed sooner and more often than the patients who did not use cannabis. These relationships persisted after statistical correction for premorbid adjustment, and alcohol and other drug use during the follow-up period.

The major cause of uncertainty about this relationship is the contribution of confounding factors, such as differences between patients who do and do not use cannabis in premorbid personality, family history and other characteristics. This is unlikely in the WHO schizophrenia study [55] and the Linszen et al. study [57], both of which used statistical methods to adjust for many of these confounders. The other difficulty is separating the contributions that cannabis and alcohol make to the exacerbation of schizophrenic symptoms. The concurrent use of alcohol is common, and the heavier the cannabis use the more likely they are to use psychostimulants and hallucinogens [25]. Only the Linszen et al. study statistically adjusted for the effects of concurrent alcohol and drug use and found that the relationship persisted. Our confidence that the effect is attributable to cannabis would be increased by replications of the Linszen et al. finding which would greatly clarify the contribution that cannabis makes to the exacerbation of psychoses.

**Intervention studies**

If we were able to reduce cannabis use among patients with schizophrenia who used cannabis, then we could discover whether their disorders improved and their risk of relapse was reduced. The major difficulty with this strategy is that it presupposes that we can successfully treat cannabis use disorders in persons with schizophrenia. Dependence on alcohol and other drugs is difficult to treat [58], and many people with schizophrenia have characteristics that predict a poor outcome, namely, they lack social support, may be cognitively impaired, unemployed, and do not comply with treatment [25,59].

There are very few controlled outcome studies of substance abuse treatment in schizophrenia [60]. A recent Cochrane review identified only six relevant studies, four of which were small [61]. The few that have been large enough [52] have not reported results separately by diagnosis. The Cochrane review found no clear evidence that supported any type of substance abuse treatment in schizophrenia over standard care.

**Self-medication**

The self-medication hypothesis is superficially plausible but the evidence in its favour is not very compelling [63]. The reasons that most people with schizophrenia give for using alcohol, cannabis and other illicit drugs are similar to those given by people who do not have schizophrenia, namely, to relieve boredom, to provide stimulation, to feel good and to socialize with peers (e.g. [25,64]). The drugs that are most often used by patients with schizophrenia are also those that are used by their peers, namely, tobacco, alcohol and cannabis.

In favour of the self-medication hypothesis is the evidence that some schizophrenic patients report using cannabis because its euphoric effects relieve negative symptoms and depression (e.g. [22,28,65]). Dixon et al. [28], for example, surveyed 83 patients with schizophrenia who reported that cannabis reduced
anxiety and depression, and increased a sense of calm but at the cost of increased suspiciousness.

Hamera et al. [66] examined correlations over 84 consecutive days between self-reported psychotic symptoms, licit and illicit drug use and medication compliance in 17 persons with schizophrenia. They found relationships only between nicotine and prodromal psychotic symptoms and between caffeine use and symptoms of anxiety and depression, but no relationships were found between psychotic symptoms and alcohol or cannabis use. Their negative results have recently been supported by Verdoux et al. [49] who found that cannabis use predicted psychotic symptoms in the following few hours but not vice versa.

The issue of cannabis potency
Cohen [67] claimed that research undertaken in the 1970s and early 1980s underestimated the adverse health effects of cannabis because it was based upon the use of less potent cannabis (0.5–1.0% THC) than was used in the United States in the late 1980s (3.5% THC in 1985–86). This claim has been repeated in the scientific media (e.g. [59,66]) and in Australia claims have been made that there has been a ‘thirty-fold’ increase in the THC content of cannabis [70].

The United States is the only country that has analysed the THC content of cannabis products over the past few decades. This shows an increase from the early 1970s to the mid-1980s but critics have argued that samples studied in the 1970s were unrepresentative of cannabis at that time. They cite data from cannabis tested in the same period by independent laboratories which show much higher THC levels. More recent US data have shown that the THC content of seizures increased from 3.3% in 1980 to 4.4% in 1998 [71,72].

A more important factor in determining exposure to THC may have been changes in patterns of cannabis use between 1970 and 2000. Survey data in Australia [73] and the United States [74] indicate that young people initiate cannabis use at an earlier age than was the case in the 1980s. Earlier initiation of use increases the risks of cannabis dependence and adverse health effects of use [75]. Regular cannabis use also makes users tolerant to the effects of THC, encouraging the use of more potent cannabis preparations [70]. Over the past two decades a large-scale illicit cannabis industry has developed in many countries, which aims to meet the demand for cannabis from daily users who prefer more potent forms of cannabis [70]. These changes in patterns of use—earlier initiation of use and more regular use of more potent cannabis products—have probably increased the amount of THC consumed by regular cannabis users [70]. In so far as this has happened, young cannabis users who initiate at an early age and subsequently use cannabis regularly are probably exposing themselves to an increased risk of experiencing psychotic symptoms. This may explain the relationship between age of initiation and risk of psychosis reported in the Dunedin birth cohort.

Summary
The evidence in favour of the hypothesis that there is a ‘cannabis psychosis’ is weak. In its favour are case series and the small number of controlled studies. Critics of the hypothesis emphasize the fallibility of clinical judgments about aetiology, the poorly specified criteria used in diagnosing these psychoses, the dearth of controlled studies, and the striking variations in the clinical features of ‘cannabis psychoses’ [76]. It is a plausible hypothesis that high doses of cannabis can produce psychotic symptoms but the evidence for a specific ‘cannabis psychoses’ is less compelling because the clinical symptoms reported by different observers have been so mixed.

There is reasonable epidemiological evidence that cannabis use exacerbates the symptoms of schizophrenia. This is supported by the findings of a number of retrospective and prospective studies that have controlled for confounding variables. It is also biologically plausible. Psychotic disorders involve disturbances in the dopamine neurotransmitter systems since drugs that increase dopamine release produce psychotic symptoms when given in large doses, and neuroleptic drugs that reduce psychotic symptoms also reduce dopamine levels [77,78]. Cannabinoids such as THC increase dopamine release in the nucleus acumbens [79].

There is now consistent evidence from prospective epidemiological studies that cannabis use precipitates schizophrenia in people who are vulnerable because of a personal or family history of schizophrenia. This hypothesis is consistent with the stress–diathesis model of schizophrenia [39,80] in which the likelihood of developing schizophrenia is the product of stress acting upon a genetic ‘diathesis’ to develop schizophrenia. There is also evidence that a genetic vulnerability to psychosis increases the risk that cannabis users will develop psychosis [17,47,49].

The most contentious issue is whether cannabis use can cause schizophrenia that would not have occurred in its absence. The estimated attributable risk in early studies was 7% [40] but higher estimates (13%) have been produced in more recent studies and one study has estimated that cannabis use is a contributory cause of 50% of cases in need of treatment [46]. The puzzle is that the treated incidence of schizophrenia, and particularly early onset, acute cases has not obviously increased during the 1970s and 1980s [81] when there have been substantial increases in cannabis use among young adults in Australia and North America [82,83].
Although there are complications in interpreting such trends [84], a large reduction in treated incidence has been observed in a number of countries which have a high prevalence of cannabis use and in which the reduction is unlikely to be a diagnostic artefact [85]. Debate has not been about whether incidence has increased, but about whether it has declined or remained stationary [86].

Australia has high rates of cannabis use among adolescents and young adults. While the majority of cannabis users will not experience psychosis as a consequence of their use, a vulnerable minority appear to be at increased risk of experiencing harmful outcomes. The epidemiological evidence now suggests that cannabis use among this vulnerable group should be discouraged where they can be identified. The Dunedin study suggests that younger age of initiation to cannabis use may increase the risk substantially.

The major challenge will be in communicating with young people about the probable psychotogenic risks of cannabis use. This task will be complicated by the conflicting interpretations of the evidence on either side of the policy debate about the legal status of cannabis. We can expect those who defend current policy to wean cannabis psychosis. Psychiatr Bull 1992;16:310 – 11.

References


