

CANNABIS AND PSYCHOSIS

Wayne Hall

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Wayne Hall

National Drug and Alcohol Research Centre
University of New South Wales, Sydney

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SUMMARY

This report reviews evidence on two hypotheses about the relationship between cannabis use and psychosis. The first hypothesis is that heavy cannabis use may cause a "cannabis psychosis" - a psychosis that would not occur in the absence of cannabis use, the symptoms of which are preceded by heavy cannabis use and remit after abstinence. The second hypothesis is that cannabis use may precipitate schizophrenia, or exacerbate its symptoms.

Evaluation of these hypotheses requires evidence of an association between cannabis use and psychosis, that is unlikely to be due to chance, in which cannabis use precedes psychosis, and in which we can exclude the hypothesis that the relationship is due to other factors, such as, other drug use, or a personal vulnerability to psychosis.

There is some clinical support for the first hypothesis. If these disorders exist they seem to be rare, because they require very high doses of THC, the prolonged use of highly potent forms of cannabis, or a pre-existing (but as yet unspecified) vulnerability. There is more support for the second hypothesis in that a large prospective study has shown a linear relationship between the frequency with which cannabis had been used by age 18 and the risks over the subsequent 15 years of a diagnosis of schizophrenia. It is still unclear whether this means that cannabis use precipitates schizophrenia, whether it is a form of "self-medication", or whether the association is due to the use of other drugs, such as amphetamines, which heavy cannabis users are more likely to use. There is better evidence that cannabis use can exacerbate the symptoms of schizophrenia. Mental health services should identify patients with schizophrenia who use alcohol, cannabis and other drugs and advise them to abstain or to greatly reduce their drug use.

CAUSE FOR CONCERN

There are good reasons to be concerned about the possibility that cannabis use may be a cause of psychotic disorders. Psychoses are serious and disabling disorders [1]. Cannabis is widely used by young Australians during late adolescence[2], and high doses of tetrahydrocannabinol - the psychoactive substance in cannabis - have been reported to produce psychotic symptoms, such as, visual and auditory hallucinations, delusional ideas, and thought disorder, in normal volunteers [3].

There are a number of hypotheses about the relationship between cannabis use and psychosis that need to be distinguished [4]. The strongest hypothesis is that heavy cannabis use causes a specific "cannabis psychosis". This assumes that these psychoses would not occur in the absence of cannabis use, and that the causal role of cannabis use can be inferred from the symptoms and their relationship to cannabis use, e.g. they are preceded by heavy cannabis use and remit after abstinence.

A weaker type of 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 bring about schizophrenia. It does not assume that the role of cannabis can be inferred from the symptoms of the disorder, or that it will remit when cannabis use ceases.

Finally, if cannabis use can precipitate schizophrenia it is also likely that it can exacerbate the symptoms of the disorder. It may exacerbate symptoms of schizophrenia (even if it is not a precipitant of the disorder) if it reduces compliance with treatment, or interferes with the effects of the drugs 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 chance is an unlikely explanation of the association; that cannabis use preceded the psychosis; and that plausible alternative explanations of the association can be excluded [5].

Evidence that cannabis use and psychosis are associated and that chance is an unlikely explanation of the association are readily available. There are a smaller number of prospective studies that show cannabis use precedes psychoses. The most difficult task is excluding the hypothesis that the relationship between cannabis use and psychosis is due to other factors (e.g. other drug use, or a genetic predisposition to develop schizophrenia and use cannabis).

Since ethical reasons preclude experimental humans studies and there are no suitable animal models, epidemiological methods must be used to rule out common causal hypotheses. These estimate the relationship between cannabis use and the risk of developing a psychosis after adjusting for variables that may affect the risk (e.g. personal characteristics prior to using cannabis, family history of psychotic illness, and other drug use). If the relationship persists after statistical adjustment, then we can be confident that it is not due to the variables for

which statistical adjustment has been made.

"A Cannabis Psychosis"

There are a substantial number of case reports of cannabis psychoses [6-18]. These describe individuals who develop psychotic symptoms or disorders after using cannabis.

Chopra and Smith [9], for example, described 200 patients who were admitted to a psychiatric hospital in Calcutta between 1963 and 1968 with psychotic symptoms following 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 the ingestion of a large dose of cannabis and there was amnesia for the period between ingestion and hospitalisation. They argued that it was unlikely that excessive cannabis use was a sign of pre-existing psychopathology because a third of their cases had no prior psychiatric history, the symptoms were remarkably uniform regardless of prior psychiatric history, and those who used the most potent cannabis preparations experienced psychotic reactions after the shortest period of use.

The findings of Chopra and Smith [9] have received some support from other case series which suggest that large doses of potent cannabis products can be followed by a "toxic" psychotic disorder with "organic" features of amnesia and confusion. These disorders have been reported from a variety of different places including: the Caribbean [19-20], India [9], New Zealand [11], Scotland [18], South Africa [14], Sweden [8, 17, 21], the United Kingdom [6-7, 13] and the United States [15-16].

These disorders have been attributed to cannabis use for combinations of the following reasons: the onset of the symptoms followed closely upon ingestion of large quantities of cannabis; the affected individuals often exhibited "organic" symptoms, such as, confusion, disorientation and amnesia; some had no reported personal or family history of psychoses prior to using cannabis; their symptoms rapidly remitted after a period of enforced abstinence from cannabis use, usually within several days to several weeks; recovery was usually complete with the person having no residual psychotic symptoms of the type often seen in persons with schizophrenia; and if the disorder recurred it was after the individual starting using cannabis.

Some commentators have been critical of this evidence [4, 22-25]. They criticise the poor quality of information on cannabis use and its relationship to the onset of psychosis, and the person's premorbid adjustment and their family history of psychosis. They also emphasise the wide variety of clinical pictures of "cannabis psychoses" reported by different observers. These weaknesses impair the evidential value of these case series.

Controlled Studies

A small number of controlled studies have been conducted over the past 20 years. Some case-control studies have either compared persons with "cannabis psychoses" with persons who have schizophrenia, or compared psychoses occurring in persons who do and do not

have biochemical evidence of cannabis use prior to presenting for treatment. Their results have been mixed.

Thacore and Shukla [26], for example, reported a case control study that compared 25 cases who had a "cannabis psychosis" with 25 controls who were diagnosed as having paranoid schizophrenia with no history of cannabis use. Their cases had a paranoid psychosis resembling schizophrenia in which there was a clear temporal relationship between the prolonged use of cannabis and the development of psychosis on more than two occasions. Patients with the "cannabis psychosis" displayed more odd and bizarre behaviour, violence, panic, and insight, and less evidence of thought disorder, than those with schizophrenia. They also responded swiftly to neuroleptic drugs and recovered completely.

Rottanburg et al [27] conducted a similar study in which 20 psychotic patients with cannabinoids in their urine were compared with 20 psychotic patients who did not have cannabinoids in their urine. Psychotic patients with cannabinoids in their urine had more symptoms of hypomania and agitation, and less auditory hallucinations, flattening of affect, incoherent speech and hysteria than controls. They also showed marked improvements in symptoms by the end of a week, whereas there was no change in the patients whose urine did not contain cannabinoids.

Chaudry et al [28] reported a comparison of 15 psychotic "bhang" users with 10 bhang users without psychosis. They found that their cases were more likely to have a history of chronic cannabis use and past psychotic episodes. They also were more likely to be uncooperative and to have symptoms of excitement, hostility, grandiosity, hallucinations, disorientation and unusual thought content. All cases remitted within 5 days and had no residual psychotic symptoms.

Mathers et al [29] reported a study of patients presenting to two London hospitals whose urine was analysed for the presence of cannabinoids. They found a relationship between the presence of cannabinoids in urine and having a psychotic diagnosis. Rolfe et al [30] reported a similar association between urinary cannabinoids and psychosis in 234 patients admitted to a Gambian psychiatric unit.

In contrast to these positive findings, a number of controlled studies have not found such a clear association. Imade and Ebie [31], compared the symptoms of 70 patients with cannabis-induced functional psychoses, 163 patients with schizophrenia, and 39 patients with mania. They reported that there were no symptoms that were unique to cannabis psychosis, and none that enabled them to distinguish a "cannabis psychosis" from schizophrenia.

Thornicroft et al [32] compared 45 cases who had a psychosis and a urine positive for cannabinoids with 45 controls who had a psychosis but either had a urine negative for cannabinoids or reported no cannabis use. They found very few demographic or clinical differences between the groups.

McGuire et al [33-34] compared 23 cases of psychoses occurring in persons whose urines were positive for cannabinoids with 46 psychotic patients whose urines were negative for cannabinoids or who reported no cannabis use. The two groups did not differ in their psychiatric histories or symptoms profile, as assessed by "blind" ratings of clinical files using the PSE (McGuire et al [33]). The cases, however, were more likely to have a family history

of schizophrenia.

Two studies have examined the relationship between cannabis use and psychotic symptoms in the general population. Tien and Anthony [35] used data from the Epidemiologic Catchment Area study to compare the drug use of individuals who reported "psychotic experiences" during a twelve month period. These psychotic experiences comprised 4 types of hallucinations and seven types of delusional belief. They compared 477 cases who reported one or more psychotic symptoms in the one 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 [36] 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.

Two studies have reported no difference in the prevalence of psychotic disorders in chronic cannabis users and controls. Beaubruhn and Knight [37] compared the rate of psychoses in 30 chronic daily Jamaican cannabis users with that in 30 non-cannabis using controls. Stefanis et al [38] reported a study of 47 chronic cannabis users in Greece and 40 controls. The small number of cases and the low prevalence of psychosis in the population make these negative findings unconvincing.

Overall Evaluation

The existence of a "cannabis psychosis" is still a matter for debate. In its favour are case series of "cannabis psychoses", and a small number of controlled studies that compare the characteristics of "cannabis psychoses" with those of psychoses in individuals who were not using cannabis at the time of hospital admission (e.g. [39]). Critics of the hypothesis emphasise 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" [24].

It is a plausible hypothesis that high doses of cannabis can produce psychotic symptoms. There is no compelling evidence, however, that there is a specific clinical syndrome that is identifiable as a "cannabis psychosis". The clinical symptoms reported by different observers have been mixed. These symptoms seem to rapidly remit, with full recovery, after abstinence from cannabis.

If cannabis-induced psychoses exist, they are rare or they only rarely receive medical intervention in Western societies (e.g. [40-41]). The total number of cases of putative "cannabis psychoses" in the 12 case series reviewed was 397 and 200 of these came from a single series (Chopra and Smith [9]) collected over 6 years from a large geographic area in which heavy cannabis use was endemic (e.g. [9]).

There are a number of likely reasons for the rarity of "cannabis psychoses" in Western societies. One is that they occur after the use of large doses of THC, or long periods of sustained heavy use. Although lifetime use of cannabis has increased in Western societies, the pattern of heavy cannabis use remains rare [2]. A second possibility (discussed below) is that cannabis psychoses only occur in persons who have a pre-existing vulnerability to psychotic disorder. A third possibility is that heavy sustained use and vulnerability are both required.

CANNABIS USE AND SCHIZOPHRENIA

Clinical studies

In case-control studies of cannabis and other psychoactive drug use among schizophrenic patients [42-43], schizophrenic patients are more likely to have used psychotomimetic drugs such as amphetamines, cocaine, and hallucinogens than other psychiatric patients [42, 44-45] or normal controls [46, 30]). The prevalence of substance use in schizophrenic patients varies between studies but it is generally higher than comparable figures in the general population [47]. Rates of alcohol and stimulant use among schizophrenic patients also appear to have increased over the past several decades[48]. These variations are probably due to differences in the sampling of patients, with younger samples of newly incident cases reporting higher rates than older samples of chronic cases. Studies have also differed in the criteria for diagnosing schizophrenia and in way that substance use has been assessed [49].

Alcohol use abuse and dependence are probably more common in the schizophrenic population than in the general population [42, 48-49]. The findings on cannabis use have been more mixed (e.g. [29, 42, 44, 49, 50]. Generally, cannabis is the next most commonly used drug after alcohol and tobacco, although it is usually used with alcohol [49, 52].

Correlates of cannabis use in schizophrenia

The controlled clinical studies disagree about the correlates of substance abuse in schizophrenia. Most have found that young males are over-represented among cannabis users (e.g. [49, 53-54]), as in the general community [55]. In some studies, substance abusers have been reported to have an earlier onset of psychotic symptoms, a better premorbid adjustment, more episodes of illness, and more hallucinations (e.g. [44, 46, 50, 54, 56]). But other well controlled studies have failed to replicate some or all of these findings [53, 57-58].

Population studies

Surveys of psychiatric disorders in the community have reported higher rates of substance abuse disorders among persons with schizophrenia. The ECA study found an association between schizophrenia and alcohol and drug abuse and dependence [55]. Nearly half of the patients identified as schizophrenic in the ECA study had a diagnosis of substance abuse or dependence (34% for an alcohol disorder and 28% for another drug disorder) [59]. These rates were higher than the rates in general population, namely, 14% for alcohol disorders [60] and 6% for drug abuse[55]. The ECA findings have also been replicated in Edmonton, Alberta [61].

More recently, Cuffel et al [53] have reported on patterns of substance abuse among 231 cases of schizophrenia identified in the ECA study. They found that the most commonly used substances were: alcohol (37%) and cannabis (23%), followed by stimulants and hallucinogens (13%), narcotics (10%) and sedatives (8%). Multiple drug use was common and the most common combinations of drugs was alcohol and cannabis (31%).

Explanations of the Association

One possible explanation of the association is that cannabis use precipitates schizophrenic disorders in vulnerable persons (e.g. [62]). Proponents of this hypothesis cite the earlier age of onset of psychotic symptoms among cannabis users (with their drug use typically preceding the onset of symptoms), their better premorbid adjustment, their fewer negative symptoms, and their better treatment response (e.g [42, 44, 63]).

Another suggestion is that the associations between cannabis use and an early onset and good prognosis are spurious. Arndt et al [56] argue that schizophrenics with a better premorbid personality are more likely to be exposed to illicit drug use among peers than persons with schizophrenia who are socially withdrawn. There is also evidence (e.g. [1, 64]) that persons 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 persons who have an insidious onset and are socially withdrawn.

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 [44].

Precipitation of Schizophrenia

The most convincing evidence that cannabis use may precipitate schizophrenia comes from a 15-year prospective study of cannabis use and schizophrenia in 50,465 Swedish conscripts [65]. This study investigated the relationship between self-reported cannabis use at age 18 and the risk of receiving a diagnosis of schizophrenia in the subsequent 15 years, as indicated by inclusion in the Swedish psychiatric case register.

Andreasson et al [67] found that the relative risk of receiving a diagnosis of schizophrenia was 2.4 times higher among those who had tried cannabis by age 18 compared to those who had not. There was also a dose-response relationship between a diagnosis of schizophrenia and the number of times that cannabis had been used by age 18. Compared to those who had not used cannabis, the risk of developing schizophrenia was 1.3 times higher for those who had used cannabis one to ten times, 3 times higher for those who had used cannabis between one and fifty times, and 6 times higher for those who had used cannabis more than fifty times.

These risks were substantially reduced after statistical adjustment for variables that were independently related to the risk of developing schizophrenia, namely, having a psychiatric diagnosis at conscription, and having parents who had divorced (as a proxy for parental psychiatric disorder). Nevertheless, after adjustment, the dose response relationship remained statistically significant. The adjusted relative risk of a diagnosis of schizophrenia for those who had smoked cannabis from one to ten times was 1.5 times, and that for those who had used ten or more times was 2.3 times, the risk for those who had never used cannabis.

Andreasson et al [65] and Allebeck [62] have concluded that cannabis use precipitates schizophrenia in vulnerable individuals.

A number of alternative explanations of the Swedish finding have been offered by other authors. 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 [66-67]. Because the diagnosis of schizophrenia was based upon a case register there was no data on how many individuals used cannabis up until the time that their schizophrenia was diagnosed. Andreasson et al [65] argued that cannabis use persisted because cannabis use at age 18 was also strongly related to the risk of attracting a diagnosis of drug abuse.

A second possibility is that schizophrenia was misdiagnosed. On this hypothesis, the excess rate of "schizophrenia" among the heavy cannabis users was due to cannabis-induced psychoses which were mistakenly diagnosed as schizophrenia [66, 67-68] examined 21 cases of schizophrenia among conscripts in the case register (8 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 six months, thereby excluding the diagnoses of transient drug-induced psychotic symptoms.

A third hypothesis is that the relationship between cannabis use and schizophrenia is due to the use of other drugs. Longitudinal studies of illicit drug use indicate that persons who had used cannabis a large number of times by late adolescence were at increased risk of subsequently using other illicit drugs, such as, amphetamine [66, 69]. Amphetamines which can produce an acute paranoid psychosis [70-72] were the major illicit drugs of abuse in Sweden during the study period [73-75]. On this hypothesis, amphetamine-induced psychoses may explain the spurious association between cannabis use and schizophrenia. The evidence that psychotic symptoms persisted beyond 6 months [68] would also seem to exclude this hypothesis.

A fourth hypothesis is that cannabis use at age 18 was a symptom of emerging schizophrenia. Andreasson et al [68] 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 [68]. Moreover, although 58% of the heavy cannabis users had a psychiatric diagnosis at the time of conscription, there was still a dose-response relationship between cannabis use and schizophrenia among those who had no such history. 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 depends upon the validity of the self-reported cannabis use at conscription. Andreasson et al [66] acknowledged that there probably was under-reporting of cannabis use because this information was not collected anonymously. They argued, however, that this would produce an under-estimate of the relationship between cannabis use and the risk of schizophrenia. This will be true if the schizophrenic and non-schizophrenic conscripts were equally likely to under-report. If, for example, pre-schizophrenic subjects were more candid about their drug use, then the apparent relationship between cannabis use and schizophrenia could be due to response bias [67]. 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.

Exacerbation of Schizophrenia

Clinical reports suggest that schizophrenic patients who continue to use cannabis experience more psychotic symptoms [76], respond poorly to neuroleptic drugs [77], and have a worse clinical course than those patients who do not [78-80]. These reports have been supported by controlled studies.

Negrete et al [81] conducted a retrospective study of the relationship between self-reported cannabis use and symptoms. They used clinical records of symptoms and treatment seeking among 137 schizophrenic patients who had a disorder of at least six months duration, and who had made three visits to their psychiatric service during the previous six months. Negrete et al [81] compared the prevalence of hallucinations, delusions and hospitalisations among the active cannabis users with that in patients who had previously used cannabis, and those who had never used cannabis. There were higher rates of continuous hallucinations and delusions, and more hospitalisations among active cannabis users. These relationships persisted after statistical adjustment for age and sex differences between the user groups.

Negrete et al [81] argued that cannabis use exacerbated schizophrenic symptoms. They rejected the alternative hypothesis that patients with a poorer prognosis were more likely to use cannabis because those who no longer used cannabis experienced fewer symptoms, and reported a high rate of adverse effects when they did use it. They also discounted the possibility that these were toxic psychoses because the minimum duration of symptoms had been six months.

Cleghorn et al [82] compared the symptom profiles of schizophrenic patients with histories of substance abuse, among whom cannabis was the most heavily used drug. Drug abusers had a higher prevalence of hallucinations, delusions and positive symptoms than those who did not abuse drugs.

Jablensky et al [64] reported a two year follow-up of 1202 first episode schizophrenic patients enrolled in 10 countries as part of a 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 periods of hospitalisation. Martinez-Arevalo et al [82] also reported that continued use of cannabis during a one year follow up of 62 DSM-diagnosed schizophrenic patients predicted a higher rate of relapse and poorer compliance with anti-psychotic drug treatment.

Linszen et al [84] recently reported a prospective study of outcome in 93 psychotic patients whose symptoms were assessed monthly over a year. Twenty four of their patients were cannabis abusers (11 were less than daily users and 13 were daily cannabis users). Despite the small sample sizes, they found that the cannabis users as a whole 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, with the daily users relapsing 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 multivariate adjustment for premorbid adjustment, and alcohol and other drug use during the follow up period.

Most but not all studies [58], indicate that cannabis use exacerbates psychotic symptoms in patients with schizophrenia. The major cause of uncertainty about this relationship is assessing the contribution of confounding factors. It may be, for example, that the difference in psychotic symptoms between schizophrenia patients who do and do not use cannabis is due to differences in premorbid personality, family history, and other characteristics [52]. This is unlikely in the WHO schizophrenia study [64] and the recent study of Linzen [84], both of which used multivariate statistical methods to adjust for many of these confounders.

The other difficulty is separating the contributions that cannabis and alcohol make to exacerbations of schizophrenic symptoms. It is rare for a schizophrenic patient to *only* use cannabis [49]. The concurrent use of alcohol is common, and the heavier their cannabis use, the more likely they are to use psychostimulants and hallucinogens. Only the Linszen et al [84] 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 [84] finding.

Intervention Studies

If we could reduce cannabis use among patients with schizophrenia who use cannabis, then we could discover whether their disorders improved and whether the risks of relapse were substantially reduced. The major difficulty with this strategy is that it presupposes that we can successfully treat substance abuse in persons with schizophrenia. Alcohol and other substance abuse are difficult to treat [85], and many persons with schizophrenia have characteristics that predict a poor treatment outcome, namely, they lack social support, they may be cognitively impaired, they are unemployed, and they do not comply with treatment [49, 52].

There are very few controlled outcome studies of substance abuse treatment in schizophrenia [86]. 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 impacts of abstinence on the course of disorders [49, 52]. The few that have been large enough [87] have not reported results separately by diagnosis.

Self-Medication

The reasons that most persons with schizophrenia give for using alcohol, cannabis and other illicit drugs are similar to those given by persons who do not have schizophrenia, namely, to relieve boredom, to provide stimulation, to feel good and to socialise with peers (e.g. [49,88-90]). The drugs that are most often used by schizophrenic patients are also those that are most readily available [48-49].

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. [42, 44, 91]). Dixon et al [44], 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.

More recently, Hamera et al [90]) have reported a time series study that 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 only found relationships between nicotine and prodromal psychotic symptoms and between caffeine use and symptoms of anxiety and depression. No relationships were found between psychotic symptoms and alcohol or cannabis use.

This study does have limitations. The difficulty of the self-monitoring task probably selected patients who were more compliant and less disordered than a representative sample of schizophrenics. There were also relatively low rates of heavy drug use. The time period of 84 days may have been too short to examine the relationship between drug use and major exacerbations of the illness, and the task of self-monitoring may have had reactive effects on drug use.

An Overall Evaluation

The epidemiological evidence is strongest that cannabis use exacerbates the symptoms of schizophrenia in affected individuals. This is supported by the findings of a number of retrospective and prospective studies which 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 [93]. Cannabinoids, such as THC, increase dopamine release [92].

It is also likely that cannabis use precipitates schizophrenia in persons who are vulnerable because of a personal or family history of schizophrenia (e.g. [22,39, 41]). This hypothesis is consistent with the stress-diathesis model of schizophrenia [39, 95] in which the likelihood of developing schizophrenia is the product of stress acting upon a genetic "diathesis" to develop schizophrenia.

Although plausible, there is very little direct evidence that genetic vulnerability increases the risk that cannabis users will develop psychosis. McGuire et al [34] reported that persons with a history of heavy cannabis use who developed a psychosis were 10 times more likely to have a family history of schizophrenia than persons with a psychosis who had not used cannabis. It is also difficult to identify a genetic diathesis in the majority of cases of schizophrenia. Having a first degree relative (parent or sibling) who has schizophrenia increases the risks of developing the disorder between 9 and 18 times [95]. But, according to Gottesman [95], 81% of persons with schizophrenia will not have a first degree relative with the disorder, and 63% will not have an affected first or second degree relative.

The most contentious issue is whether cannabis use can cause schizophrenia that would not have occurred in its absence. One cannot rule it out but it is unlikely to account for more than

a minority of cases. Most of the 274 conscripts who developed schizophrenia had not used cannabis, and only 21 were heavy cannabis users and at most 7% of cases of schizophrenia could be attributed to cannabis use. The *treated* incidence of schizophrenia, and particularly early onset, acute cases, has declined (or remained stable) during the 1970s and 1980s [94] when cannabis use increased among young adults in Australia and North America [2]. Although there are complications in interpreting such trends [97-99] a large reduction in treated incidence has been observed in a number of countries and it cannot be explained as a diagnostic artefact [100].

IMPLICATIONS FOR PATIENTS AND THEIR FAMILIES

Mental health services should identify patients with schizophrenia who use alcohol, cannabis and other drugs, and discuss its impact on their disorder with them. Although this paper has primarily focussed on cannabis use, the role alcohol should not be neglected. Cannabis is most often used with alcohol and heavy alcohol use is a stronger predictor of psychotic symptoms (OR = 7.9) than regular cannabis use (OR= 2.0) [35].

Patients whose drug use may be exacerbating their symptoms should be advised to trial abstinence. Advice to abstain or to substantially reduce use may be better received if accompanied by alternative suggestions about how to deal with the negative symptoms and depression [52, 49]. If they are not prepared to abstain, they may be prepared to reduce the frequency and quantity of drug use [52]. A positive effect on well-being and social functioning may motivate patients to consider longer term abstinence or a sustained reduction in use.

In assisting patients who wish to become abstinent, we may need to modify some traditional treatment methods [49, 52]. Alcoholics Anonymous and Narcotics Anonymous group based approaches [52] may pose difficulties for many patients with schizophrenia who find social interaction difficult. These groups may also be opposed to using anti-psychotic medication.

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