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Cannabis and Psychosis

Is there Epidemiological Evidence for an Association?

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A review of the evidence shows that there is no convincing support for a separate clinical diagnosis of 'cannabis psychosis'. Cannabis can, however, produce brief acute organic reactions and, in moderate to heavy doses, psychotic episodes in clear consciousness. Ingestion in naive users or increasingly heavy use in habitual users can precipitate a schizophreniform episode. Heavy users may have an increased risk of developing schizophrenia in the subsequent 15 years. Well controlled, longitudinal studies are required to explore these associations further and their possible aetiological significance.

Since antiquity, a 'cloud of witnesses' (Lewis, 1968) have attested to the existence of forms of psychosis directly related to cannabis use, and the terms 'cannabis, marihuana, bhang and hasheesh psychosis' have entered the psychiatric literature (Warnock, 1903; Ames, 1958; Talbott & Teague, 1969; Thacore, 1973; Ghodse, 1986).

Previous reviews of the possible association between cannabis and psychosis have proposed six types of association (Lewis, 1968; Weil, 1970; Harding & Knight, 1973; Treffert, 1978; Tunving, 1985; Ghodse, 1986). Cannabis may cause psychoses *de novo*. It may reveal a previously latent psychosis. Cannabis may precipitate a relapse of a pre-existing psychosis. Established psychotic mental disorder may lead to an increased intake of cannabis. There may be a spurious relationship. Finally, there may be no relationship between psychosis and cannabis.

These reviews have, however, failed to make three vital distinctions. Firstly, they have not adequately separated organic from functional psychotic reactions to cannabis. Secondly, they have insufficiently discriminated between psychotic symptoms and the syndromes of psychosis. Thirdly, they have not balanced the weight of evidence for and against the category of 'cannabis psychosis'.

In this paper I assess the strength of the contention that cannabis and psychotic disorders are associated by using the epidemiological criteria suggested by Hill (1965): the strength of the association, its consistency, specificity, temporality, biological gradient, plausibility and coherence, and the experimental evidence. I also consider the methodological problems of the studies cited.

Reference is not made here to the extensive literature on the neurological, psychological, psychopharmacological, neuropathological, tolerance and dependency aspects of cannabis abuse, which have been thoroughly reviewed elsewhere (Wert & Raulin, 1986*a*,*b*; Ashton, 1987; Cambell *et al*, 1971; Renault *et al*, 1974; Tennant, 1986).

Strength of the association

In a superb study of the risk of developing a psychotic disorder in relation to cannabis use, Andreasson *et al* (1987) followed up a cohort of 45 570 Swedish men for 15 years after conscription into military service in 1969–70. Data on illicit drug usage had been collected on entry to the army, with a response rate of 93%. Of the total sample, 9.4% had used cannabis and 1.7% were classed as 'high consumers', having used cannabis on more than 50 occasions. Fifteen-year follow-up data were drawn from the national registers of death and psychiatric cases. The relative risk of schizophrenia for 'high consumers' was 6.0 compared with those who had never used the drug. Over half (430/730) of these 'high consumers', however, had a psychiatric diagnosis other than psychosis at conscription, and when this confound was controlled by stratified analysis, the relative risk was more than halved to 2.9. Overall, this report provides strong evidence that cannabis is an independent risk factor at the population level for the development of schizophrenia.

Consistency of the association

By 'consistency', Hill refers to an association that has been "repeatedly observed by different persons, in different places, circumstances and times". Cannabis was first related directly to insanity by Ibn Beitar writing in Egypt in 1235 (Warnock, 1903). At this time, Makrizi (Warnock, 1903) described that a "general corruption of sentiments and manners ensued, modesty disappeared, every base and evil passion was openly indulged in". The Indian Hemp Drugs Commission (1894) found that "excessive use indicates and intensifies instability of the mind: it may even lead to insanity". From the West Indies, Barnes, superintendent of the lunatic asylum of British Guyana, wrote that "these patients are the most acutely insane amongst the inmates of the public asylum" (Warnock, 1903). Writing in Ranchi, India, Dhunjibhoy (1930) unequivocally stated

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that "the hemp drug is a direct cerebral poison . . . with regard to injurious tendencies in the causation of insanity".

More recent accounts of the association have emerged from South Africa (Ames, 1958; Rottanburg *et al*, 1982), Jamaica (Beaubrun & Knight, 1973), Denmark (Knudsen & Vilmar, 1984), Canada (Negrete *et al*, 1986), Sweden (Palsson *et al*, 1982), Britain (Carney *et al*, 1984) and from among American servicemen in West Germany (Tennant & Groesbeck, 1972) and Vietnam (Talbott & Teague, 1969). Geographically, cannabis has therefore been widely related to mental disorder. Historically, it has been linked with insanity in early reports, and to more specific forms of psychosis during the last century. In sum, these reports fulfil the criterion of consistency.

Specificity of the association

Case reports and series have described either psychotic symptoms or syndromes associated with cannabis use.

Psychotic symptoms

Some studies have shown psychotic symptoms in well subjects. (These studies together with others of symptoms in out- and in-patients are listed later in Table II.) Tart (1970) itemised common reactions to cannabis among 153 well Californian students who completed an anonymous questionnaire. A wide range of sensory disturbances was reported by most respondents in the visual, auditory, tactile, gustatory and olfactory modalities. Becoming 'somewhat paranoid' was rated positively by 80% of the students, and 20% agreed that they were sometimes "taken over by an outside force or will which is hostile". A majority of the American college students interviewed by Keeler (1968) had experienced ideas of persecution while intoxicated with cannabis, and a quarter reported visual hallucinations (Keeler *et al*, 1971).

Derealisation has also been described during cannabis intoxication (Ames, 1958): indeed, two small case series have reported prolonged depersonalisation after cannabis ingestion (Symanski, 1981; Keshavan & Lishman, 1986).

A case-control study in Jamaica (Beaubrun & Knight, 1973) found that a higher proportion of chronic cannabis users than non-users had experienced auditory or visual hallucinations, mainly occurring on first use of the drug. Moderate to heavy doses of cannabis have therefore been shown to produce a wide variety of usually brief psychotic symptoms. Moreover, a range of other drugs, including nitrous oxide, may produce similar psychomimetic actions, and indeed may serve as useful models to precipitate brief psychotic symptoms (Tart, 1969; Block *et al*, 1988).

Psychotic syndromes

Organic psychoses

Acute organic reactions to cannabis ingestion are well characterised. The cardinal features are mild impairment of consciousness, distortion of time sense, a dream-like euphoric state, progressing to a fragmentation of thought processes and to hallucinations, and were reviewed by Lishman (1978). Weil (1970) proposed that this 'toxic psychosis' was more often found after oral ingestion than smoking. He considered that its manifestations were "quite constant and should be unmistakable" and included disorientation, confusion, auditory and visual hallucinations. The episodes were brief, followed ingestion, and had good outcome.

Chopra & Smith (1974) gave support to this syndrome, which they described as along a continuum from "an acute confusional state which often developed into a full-blown toxic psychosis". Patients without a past psychiatric history showed complete remission within a few hours to a few days. Table I shows studies associating cannabis use with acute organic reactions.

In Sweden, Palsson *et al* (1982) reported 11 patients with cannabis-associated psychoses whose common features were fluctuating mood, poor concentration and orientation, auditory and visual delusions with persecutory delusions. Although these features would be in keeping with a diagnosis of acute organic reaction, the authors suggested that they were more adequately described as cycloid psychoses.

The evidence for *chronic* organic reactions is less compelling (Winkler, 1970). Lewis (1968) thought that most studies gave insufficient details to warrant retrospective diagnoses, but that "in those who do, there are instances of persistent confusional syndromes shading off with the passage of time into chronic dementia, in which cannabis seems to have been the major cause". Spontaneous recurrences of the symptoms of acute intoxication may be relatively frequent after drug discontinuation (Keeler *et al*, 1968).

TABLE I
Studies associating cannabis use with acute organic reactions[1]

Author (date)	*Location*	*Subjects (n)*	*Design*	*Cannabis report by:*	*Comments*
Chopra & Smith (1974)	India	In-patients (200)	Descriptive	Self & informant	More acute onset associated with high potency
Talbott & Teague (1969)	Vietnam	US soldiers (12)	Descriptive	Self	Impaired attention span, concentration, and judgement, with fragmented thinking and persecutory features

1. Symptoms described in both studies comprised disorientation, amnesia, and confusion. Diagnostic criteria were given in neither study.

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TABLE II
Clinical studies associating cannabis use with psychotic symptoms

Author (date)	*Location*	*Subjects (n)*	*Design*[1]	*Symptoms described*[2]	*Comments*
Altman (1973)	Missouri	In-patients (158)	Descriptive	RD, VB & PD	No controls used
Beaubrun & Knight (1975)	Jamaica	Chronic users	Case control	S	Visual hallucinations more common in cannabis users
Carney *et al* (1984)	London	In-patients (9)	Descriptive	D & A	5/9 patients black, great variety of psychoses described
Edwards (1983)	London	Out-patients (1)	Case report	S, LM & DP	
Keshavan & Lishman (1986)	London & Bangalore	In-patients (1)	Case report	VB, S & LM	Prolonged depersonalisation after cannabis use described
Keeler *et al* (1971)	Charleston, USA	Well students (42)	Questionnaire	RD, VB & S	Minor perceptual changes most commonly described
Tart (1970)	Davis, USA	Well students (153)	Interview	PD, S, LM & VH	Visual and auditory perceptual changes most commonly reported
Thacore (1973)	Lucknow, India	In-patients (4)	Case reports	RD, S, VH, PC & D	'Bhang psychosis' described in susceptible subjects
Thacore & Shukla (1976)	Lucknow, India	In-patients (25)	Case-control	RD, S & A	Paranoid schizophrenic controls (25). Schizophrenic disorder absent in cases of cannabis related to psychosis
Treffert (1978)	Winnabago, USA	In-patients (4)	Case reports	RD, S, PC & D	Treatment-controlled schizophrenic out-patients relapsed after cannabis use

1. All studies relied on self-report of cannabis use, and none gave the diagnostic criteria used.
2. RB = religious behaviour, VB = violent behaviour, PD = persecutory delusions, S = suspiciousness, LB = labile mood, DP = depersonalisation, VH = visual hallucinations, PC = poor concentration, D = depression, A = anxiety.

There is conflicting evidence on the "vexing question" (Hollister, 1988) of whether chronic cannabis use can lead to an 'amotivational state'. Cambell (1976) found no conclusive evidence of such a syndrome. This is supported by the review of Wert & Raulin (1986*b*) of the 15 studies of chronic cerebral effects of cannabis. Despite the reported chronic effects, closer analysis revealed no clinically or statistically significant consequences of chronic cannabis use.

Functional psychoses

Dhunjibhoy (1930) classified the 'hemp psychoses' into acute mania, chronic mania and dementia. Acute mania related to cannabis, he wrote, is characterised by auditory and visual hallucinations which "refer, as a rule, to beautiful women who are supposed to talk to and copulate with the patients".

More scientifically, clinical studies have attempted to relate cannabis ingestion to psychotic syndromes and their symptoms (see Tables II and III). In a comparison of 20 psychotic in-patients who had high urinary cannabinoid levels and 20 controls in Cape Town, Rottanburg *et al* (1982) assessed the admission mental state using the standardised Present State Examination (PSE; Wing *et al*, 1974). The cannabis group displayed a different pattern of symptoms, with more hypomania and agitation, less affective flattening and incoherence of speech, and fewer auditory hallucinations. When the symptoms were analysed by the computerised CATEGO program (Wing *et al*, 1974), however, six patients were assigned to the class 'manic–depressive psychosis, manic type' (compared with three controls), while 10 were described as 'paranoid schizophrenic' (compared with 15 controls), although controls had been matched to cases by clinical diagnosis. The authors do not state whether the diagnostic classes derived were of narrowly defined cases (M+ and S+ respectively). Thus, the majority of cases fulfilled the cross-sectional criteria for existing categories of functional psychosis, most being schizophrenic, and a separate category of 'cannabis psychosis' was not warranted on phenomenological grounds. Compared with the control group, course and outcome were more favourable for cases, whose symptoms showed rapid resolution within one week.

This rapid resolution of symptoms was also found by Carney *et al* (1984) (Table II) in a case series of nine patients. Three patients had 'manic bouts' in which religious and political themes were prominent. Most of these patients were admitted compulsorily, took discharge against advice, did not attend for follow-up, and recurrence commonly followed further cannabis use.

Knight (1976) has discussed a series of 13 patients with 'marijuana-modified mania', in which regular cannabis users increased the doses they consumed after the onset of

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symptoms of mania. There were no signs of disorientation or clouding of consciousness. Unfortunately, the author did not report specific symptom patterns, or use a standardised rating scale to establish diagnosis.

In brief, there is some fairly weak evidence from small case series and case-control studies that patients admitted with psychotic conditions who have recently taken cannabis may manifest some symptoms of hypomania more frequently than non-using psychotics. In view of the small patient numbers in all the studies reviewed in this section, and, with the exception of Rottanburg *et al*'s (1982) study, in the absence of standardised assessment techniques, there is no convincing evidence that the full syndrome of hypomania occurs more frequently in cannabis users.

Distinct from the acute organic reactions to cannabis, a number of authors have described schizophreniform psychoses in clear consciousness. Thacore (1973), from four case reports, suggested that the common features were a hostile perception of the environment, fearfulness, delusions of persecution, and auditory and visual hallucinations. He suggested that this clinical picture was distinct from paranoid schizophrenia. In a detailed report by a patient of his experience using cannabis, Edwards (1983) states "I was getting very paranoid, dope makes you paranoid anyway".

Severe cannabis-specific persecutory reactions are rare. Tennant & Groesbeck (1972) (Table III) studied the 32 000 US soldiers in West Germany in 1970. Nearly half had used cannabis, and 16% continued to use it at least three times a week. Of these 5120 soldiers, over a three-year period, 720 were seen by the army medical officers with cannabis-related problems. Despite the fact that many soldiers consumed an equivalent of 500 to 6000 cannabis cigarettes each month, only 115 received a diagnosis of schizophrenic reaction, but in only three cases was cannabis used without other illicit drugs or alcohol. A similar study of US servicemen in Vietnam (Talbott & Teague, 1969) reported 12 cases of acute toxic reactions, ten of whom exhibited paranoid ideation. This evidence is weakened by the finding that half of cannabis contraband seized in Vietnam contained opiates.

Is there evidence that cannabis can be specifically associated with the development of paranoid schizophrenia? In a comparison between 25 Indian cases of 'cannabis psychosis' in clear consciousness and 25 cases of paranoid schizophrenia, Thacore & Shukla (1976) (see Table II) proposed that there were considerable differences in the clinical features. The former displayed more bizarre and violent behaviour, more panic reactions and far less thought disorder. The weight of this evidence is limited by non-blind rating, non-standardised diagnoses of schizophrenia, and the absence of corroborating urinalysis of cannabinoids.

The best support for a specific association between cannabis and schizophrenia is again drawn from the cohort study of Swedish servicemen (Andreasson *et al*, 1987), which showed that a small proportion (1%) of cannabis-using soldiers went on to present with schizophrenia – more than twice the rate found in non-users. The authors do not, however, report whether any specific subtype of schizophrenia was over-represented, whether the relative risks of any other forms of psychosis were increased, or indeed whether the patients were using cannabis at the time of diagnosis.

When examined critically, these papers together suggest that there is some weak evidence that long-term or heavy users of cannabis may occasionally develop acute psychoses in clear consciousness with paranoid and hallucinatory features, and showing behavioural disturbance. The association is diluted, however, by inadequate reporting of organic features, by non-blind rating, and by the strong suspicion that the cannabis ingestion may have been accompanied by use of other illicit drugs or alcohol.

Weighing the evidence, the following points emerge. Among already psychotic patients, cannabis use appears fairly frequently to be associated with particular symptoms of schizophrenia and manic–depressive psychosis, most notably hypomanic mood, agitation, hallucinations, and delusions of persecution. There is not good support for the idea that the full syndrome of hypomania is related to cannabis use, but there is strong preliminary evidence from the Swedish servicemen study that up to 10% of all cases of schizophrenia could be attributed to frequent, heavy cannabis use.

Temporality of the association

By temporality, Hill (1965) means "which is the cart and which the horse?" Most studies have assumed that if a causal association does exist between cannabis and an episode of psychosis, then, in the absence of reported prospective studies, it remains to be established which comes first.

Work supporting the view that cannabis use precedes the expression of psychoses has usually relied upon self-report to establish antecedence. Davison & Wilson (1972) comment upon one case in which cannabis preceded the onset of a paranoid psychosis. Thacore (1973) has described four cases of psychotic reactions to 'bhang' (cannabis resin) where there was good evidence that the episode followed prolonged and increasingly heavy ingestion. Similarly, Andreasson *et al* (1987) have clearly established that relatively heavy use in early adulthood made a later schizophrenic episode more likely.

Conversely, there is considerable anecdotal evidence that patients may increase their cannabis use after the prodromal or full onset of an acute psychotic episode. A comparative study of Asian cannabis users and controls in Athens found that users were four times more likely to have a past psychiatric history (Stefanis, 1978). Harding & Knight (1973) describe four Jamaican patients who remained asymptomatic with chronic moderate cannabis use, but who markedly increased their usage several days after the onset of hypomanic symptoms. They described the condition as 'marihuana-modified mania'. Suggestive data drawn from a survey of white college students in St Louis found that among the 100 users, 50% had received psychiatric treatment compared with 40% of their non-cannabis-using friends (Halikas *et al*, 1972). Among users, four-fifths of episodes preceded initial cannabis use. The authors do not, however, give sufficient detail to establish the proportion of these episodes that were psychotic.

The evidence relating cannabis and psychosis over time is again beset by the limitations of the data. Firstly, there is widespread agreement that high doses of cannabis precede acute

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TABLE III

Clinical studies associating cannabis use with psychotic syndromes

Author (date)	*Location*	*Subjects (n)*	*Design*	*Cannabis report by:*	*Diagnostic criteria*	*Syndrome described*[1] *schizophrenic*	*affective*	*paranoid*	*other*	*Comments*
Andreasson *et al* (1987)	Sweden	Soldiers (45 570)	Cohort	Questionnaire	ICD-8	+				High cannabis users have relative risk of 6.0 for developing schizophrenia compared with non-users
Breakey *et al* (1974)	New York	In-patients (46)	Case-control	Self & informant	Stated	+				Earlier onset among cannabis-using schizophrenics
Davison & Wilson (1972)	Newcastle, UK	In-patients (1)	Case report	Self	Not given				+	Case of psychotic relapse precipitated by cannabis
Halikas *et al* (1972)	St Louis, USA	Cannabis users (100)	Comparison	Self	'Standard' (not given)		+			Psychiatric problems preceded cannabis use
Harding & Knight (1973)	Jamaica	In-patients (4)	Case reports	Self	Not given		+			Onset of mania preceded manic phase
Knight (1976)	Jamaica	In-patients (223)	Descriptive	Self	Not given	+	+		+	24% of all in-patients with a functional psychosis had used cannabis; no control group
Knudsen & Vilmar (1984)	Denmark	In- & day-patients	Descriptive	Self	'Crows' criteria'	+				Schizophrenia relapse precipitated by cannabis use
Negrete *et al* (1986)	Montreal, Canada	In-patients (137)	Comparison	Urine assay	ICD-9	+				Cannabis-using schizophrenics showed more delusions, hallucinations and hospital visits
Palsson (1982)	Lund, Sweden	In-patients (11)	Descriptive	Self	Not given				+	Mixed affective and schizophrenic symptoms, similar to cycloid psychoses; cases had good outcome
Rottanburg (1982)	S. Africa	In-patients (20)	Case-control	Urine assay	ICD-9	+	+	+		Cannabis-using psychotics had shorter course; symptoms of hypomania more common in cannabis users
Tennant & Groesbeck	W. Germany	US army (36 000)	Descriptive	Self	Not given	+				36 000 soldiers: cannabis prevalence 46% in 3 years; in only 3 cases cannabis used without other drugs

1. + = syndrome described.

organic toxic reactions. But these mainly small, unrepresentative samples have not established that cannabis recurrently precedes psychotic episodes. Where a psychotic reaction does occur the period of use before symptoms development is shorter for more potent preparations of cannabis (Chopra & Smith, 1974). Until more satisfactory information becomes available from prospective studies, the precise nature of the temporal relationship will remain unclear.

Biological gradient of the association

If cannabis is causally associated with psychoses we may expect to find in the clinical reports a dose–response relationship of greater morbidity with higher dose. Unfortunately, dose measurement of cannabis is notoriously unreliable except under experimental conditions (Renault *et al*, 1974), and the cannabis effect is often confounded by concurrent use of other psychoactive substances (Breakey *et al*, 1974).

Among non-psychotic users there is clear evidence that higher doses produce perceptual changes, thought disturbance and auditory and visual hallucinations (Keeler *et al*, 1971). From a study of 720 cannabis-using US soldiers stationed in West Germany, Tennant & Groesbeck (1972) proposed a dose–response scheme. Using less than 12 g of cannabis a month was usually associated only with minor respiratory ailments. Monthly doses of up to 25 g were found in men who developed acute toxic reactions, and in three cases, a dose of up to 50 g was described in association with schizophrenic reactions. Higher doses still (up to 600 g monthly) produced a chronic intoxicated state.

This dose effect is supported by Chopra & Smith (1974) who compared symptom development among users of different preparations of cannabis in Calcultta. Hashish, or the cannabis resin, more often produced psychotic reactions than the ingestion of leaves. Expressed in epidemiological terms, the relative risk of developing schizophrenia in the fifteen years after conscription to the Swedish army (Andreasson *et al*, 1987) was positively correlated with the number of occasions that cannabis had been used by the time of conscription.

As well as potentially affecting the presence of psychotic symptoms, cannabis may influence their severity. Negrete *et al* (1986) in Montreal interviewed 137 out-patients with an ICD-9 (World Health Organization, 1978) diagnosis of schizophrenia. They constructed a composite score of the severity of psychotic symptoms, and demonstrated that this was positively associated with the extent and recency of cannabis use. But as their 'active user' category contained both those with positive urinary assays and those who admitted consuming cannabis within the previous six months, this evidence does not directly bear on the issue of whether cannabis directly precipitates these more severe schizophrenic episodes.

To summarise, there is firm evidence of a dose–response relationship in the development of the toxic acute organic syndrome, and there is reasonable support for the view that more potent preparations precipitate more severe and rapid reactions. Higher doses have not been convincingly shown to trigger immediate functional psychotic episodes more often, although it appears that in the longer term, schizophrenia occurs more often than would be otherwise expected in heavy users.

Experimental evidence for the association

Experimental conditions may be expected to clarify issues not accessible to cross-section or retrospective clinical descriptions, and are summarised in Table IV. Isbell *et al* (1967) administered the delta-9 isomer of trans-tetrahydrocannabinol (a chemical equivalent of cannabis) to 10 prisoners. Oral doses of up to 120 μg/kg produced euphoria, changes in sense of time, auditory and visual perception and those in excess of 300 μg/kg produced visual and auditory hallucinations, depersonalisation and derealisation. A dose–response relationship was established with these psychotic symptoms. A few subjects had idiosyncratic psychotic responses at low doses, and these reactions were reproducible for given individuals. In a controlled administration of marijuana to seven normal volunteers in Chicago, all showed impairment of concentration and orientation at relatively low doses, and again an idiosyncratic toxic psychosis was noted in a minority (Renault, 1974).

Habitual cannabis users have been shown under experimental conditions to have less perceptual impairment than casual users when challenged with cannabis, and in this study too, one naïve subject experienced a brief paranoid episode (Meyer *et al*, 1971). Ames (1958) administered cannabis to ten junior doctors. There was a marked individual variation in response, and one developed hypomanic symptoms with delusions of persecution and was treated with intramuscular chlorpromazine.

The experimental data available, although somewhat limited, strongly support the view that cannabis precedes and produces symptoms of psychosis, that this occurs usually only at high doses and possibly especially in those who are not habitual users, and that a small proportion of individuals seem to develop more severe idiosyncratic psychotic syndromes at relatively low doses.

Methodological considerations

The implications of the studies reviewed here are severely limited by inadequacies in their research design. Imprecision has been introduced by the characterisation of subjects, the selection of controls, the diagnostic classifications used, confounding factors, the limited statistical power of small studies, and oversimplified models of causal associations.

Most studies cited here have started from the presumption of an association between cannabis and psychosis. Highly selected case series have been repeatedly described with neither reference to base population rates of cannabis use, nor to the expected rates and clinical variations in organic and functional psychoses. They have argued circularly that the condition whose existence was presumed could then be inferred. Moreover, the studies reviewed describe a vast range of subjects using cannabis, ranging from volunteer medical staff to imprisoned drug offenders. Biographical data, especially past psychiatric and family history, are incompletely reported (Tsuang *et al*, 1982). The selection of controls has often failed to clarify a possible relationship.

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TABLE IV
Experimental studies associating cannabis use with psychotic symptoms

Author (date)	*Location*	*Subjects (n)*	*Cannabis dose*	*Symptoms described*[2]	*Comments*
Ames (1958)	S. Africa	Volunteer doctors (10)	0.06 g	ATS,RD,PD, LM,E,D&TD	Manic symptoms reported in one subject given 0.48 g by mistake
Clark (1970)	Utah, USA	Graduates (18)	0.66 mg/kg THC[1]	S	
Isbell *et al* (1967)	Kentucky, USA	Prisoners (ex-opiate addicts) (10)	50–480 μg/kg THC[1]	RD,LM,E&VH	Idiosyncratic psychotic responses found with low cannabis doses
Meyer *et al* (1971)	Boston, USA	Cannabis users (12)	2.25 mg THC[1]	RD	Cannabis effect related to history of use, strong placebo effect
Renault *et al* (1974)	Chicago, USA	Volunteers (7)	6.5–12.2 mg THC[1] equivalent	LM	Idiosyncratic brief toxic psychosis described

1. THC = tetrahydrocannabinol.
2. ATS = altered time sense, RD = religious delusions, PD = persecutory delusions, LM = labile mood, E = euphoria, D = depression, TD = thought disorder, VH = visual hallucinations, S = suspiciousness.

No study has systematically matched controls with cases for presumed confounding factors. Accounts of the adverse effects of cannabis among women are also notably absent from the literature.

The clear definition of the two variables of interest has only recently been a feature of reports in this field. The use of non-standardised clinical diagnoses, without symptom profiles, allows only limited inferences to be drawn. Similarly, the ascertainment and measurement of cannabis ingestion have been notoriously difficult. Lifetime estimates rely on self-report with both recall bias and the unquantified effect of a reluctance to admit use of an illicit drug. Further, preparations vary widely in their potency.

The influence of possible confounding factors have, with the exception of the Andreasson *et al* (1987) study, been omitted from the studies reviewed. Andreasson *et al* did indicate that indices of poor childhood and adult social adjustment were independently associated with both cannabis use and the development of schizophrenia. The confounding variables most commonly ignored are ethnic group and concurrent alcohol and substance abuse. Indeed, several studies report an apparent cannabis effect in the presence of poly-drug abuse among many of the patients (Talbott & Teague, 1969). Furthermore, in several studies, selection bias may have acted to over-represent cases of presumed cannabis-related psychosis among Afro-Caribbean patients. Ethnic group has too rarely been controlled for.

In addition, the scale of the majority of reports severely limits their ability to detect any true differences between psychoses in cannabis users and in the comparison groups. Where such differences are reported, they are interpreted to support an oversimplified model of causation in which cannabis alone is presumed to be a sufficient precipitant of the psychotic episode. An interactive model seems more plausible in which aetiological factors act synergistically. It has been suggested, for example, that in constitutionally vulnerable individuals, a psychosis can be triggered by low doses of cannabis, especially when consumed at a susceptible age (Estroff & Gold, 1986). Equally, a prodromal episode of hypomania may induce an increased cannabis consumption which hastens or exacerbates the relapse. In these terms, cannabis may be seen as an induction agent which is necessary but rarely sufficient to produce a functional psychotic syndrome.

Conclusions

Carefully weighing the evidence relating cannabis to psychosis yields the following points. Cannabis can produce a brief acute organic reaction. Evidence for chronic organic reactions is sparse. Moderate to heavy doses can produce psychotic symptoms in clear consciousness, especially auditory and visual hallucinations and persecutory delusions. The evidence that cannabis can cause the syndrome of hypomania is not convincing. Cannabis ingestion in naïve users or increasingly heavy consumption among habitual users may occasionally precipitate a schizophreniform episode, but these are usually relapses of known cases, or infrequent idiosyncratic reactions. At the population level, groups of heavy users probably have a higher risk of developing schizophrenia in the subsequent fifteen years, but this finding has not yet been replicated. Given this, there is no convincing support for a separate clinical diagnosis of 'cannabis psychosis'.

The author recommends, pending the outcome of controlled studies, that clinicians consider discontinuing use of the term 'cannabis psychosis'. In clinical practice, the use of the following ICD-9

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diagnoses is suggested. Organic reactions should be termed 'acute and subacute confusional states' (293.0 and 293.1). Acute idiosyncratic reactions should be categorised as 'pathological drug intoxication' (292.2) and subacute reactions as 'paranoid and/or hallucinatory states induced by drugs' (292.1). Clear affective or schizophrenic psychoses should be accorded their usual ICD code. Cannabis dependence, withdrawal and non-dependent use should be described by the categories 304.3, 292.0 and 305.2 respectively.

What information should be collected to elucidate this association? Firstly, in normal clinical practice, where there is a suspicion that cannabis may be implicated, every effort should be made to document the full personal, family, social, drug and alcohol history with details of duration, frequency and dose of ingestion. Information on the course and outcome, together with the use of standardised mental and cognitive state examinations, will greatly facilitate future case-note analysis. Wherever possible, urinary assays should be performed.

Further case reports are not likely to be of benefit. Case-control studies, with cases ascertained either retrospectively or prospectively, will enable the relative risk of developing psychoses for cannabis users to be compared with non-users. Great care will need to be taken in controlling the data for ethnicity, social class and other substance abuse. Population surveys could provide valuable evidence on the prevalence of cannabis use within defined areas. Cohort studies, using either the historical approach of Andreasson *et al* (1987) or a conventional prospective design, will offer the most compelling evidence if based on standardised diagnostic criteria and quantitative estimation of cannabis consumption. Finally, where ethnically acceptable, clinical trials of administering cannabis to psychotic patients should focus on dose–response effects, and further characterisation of idiosyncratic responses.

The methodological tools are now available to investigate possible risk factors for mental disorders: the precise use of these tools will shape our understanding of the influence of cannabis upon the psychoses.

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