

## Cannabis and Psychopathology : Update 2004

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### ABSTRACT

The study of cannabis use and psychopathology remains an interesting area from both academic and pragmatic perspectives. This article provides an update on the progress made in this area over the past decade or so. Psychopathology and psychiatric syndromes associated with cannabis use that have received research attention in recent years include cannabis withdrawal, cannabis and psychotic disorders (especially schizophrenia), depression, anxiety, and cognitive impairment. Status of a specific cannabis withdrawal syndrome and a specific 'cannabis psychosis' remains controversial. Current evidence indicates that there is a clinically significant association between cannabis use disorders and psychotic syndromes, depression, anxiety and possibly mild cognitive impairment. However, the nature of this association is often not clear. Several hypothesis related to the cannabis-schizophrenia association are examined. Cannabis use might be casually related to the later development of schizophrenia in an indirect way in a few heavy users, but more commonly, its use may precipitate disorders in persons who are vulnerable to developing psychosis and worsen the course of the disorder.

**Key Words :** Cannabis, psychopathology, withdrawal, psychosis, schizophrenia, depression, mania, anxiety.

### Introduction

Cannabis is the world's most commonly used illicit drug, with approximately 200 to 300 million regular users. It occupies fourth place in worldwide popularity among psychoactive drugs, after caffeine, nicotine and alcohol (Macfadden et al., 2000). The prevalence of lifetime use of cannabis by young adults has increased in many developed countries over the past several decades (Hall et al., 1999). The ready availability of the drug, the increasing social disapproval of cigarette smoking, stern drinking laws, and perceptions that cannabis is safe or less harmful than cigarettes or alcohol may explain these changes (Rey and Tennant, 2002).

Cannabis is also associated with significant psychiatric comorbidity. In a review published in this Journal 10 years ago (Basu et al., 1994), the authors had reviewed the status of various psychopathologies associated with cannabis. A lot of new research has been published since then, partly settling some of the old controversies while raising new ones. The topic is relevant because psychopathology and comorbid psychiatric disorders are still very common among heavy cannabis users in treatment settings, both in India (Sarkar et al., 2003) and abroad (Arendt and Munk-Jorgensen, 2004). It was felt that an update was necessary to take a stock of the situation and to direct new research in this area. In the current update we specifically focus on research in this area over the last 10-15 years. Only very

relevant articles or those of historical interest published before that period are cited.

The search strategies for this update included both search of electronic databases as well as manual search of relevant publications or cross references. Electronic search included both PUBMED searches and searches using other search engines. Cross-searches of key references (both electronic and hand-search) often yielded other relevant material. The search terms used (in various combinations) were: cannabis, marijuana, cannabinoids; use, abuse, dependence, withdrawal; psychopathology, psychiatric syndromes; psychosis, schizophrenia, depression, mania, anxiety; cognition, neuropsychology, cognitive impairment; flashback, amotivational syndrome. While it cannot be guaranteed that all relevant articles could be located, considering the huge number of publications, an attempt has been made to provide a balanced update within the constraints of search strategies employed and the demands on journal space. Although there is a plethora of laboratory and biochemical studies using cannabinoids, both exogenous (cannabis-derived) and endogenous (e.g., anandamide), we have focused mostly on the clinical studies keeping in view the scope of the subject covered.

### Cannabis and Psychopathology

Both DSM-IV-TR (American Psychiatric Association, 2000) and ICD-10 (World Health Organization, 1992) have

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given various categories of disorders associated with the use of cannabis, with ICD-10 having a wider approach. The most important thing which is apparent from the classification is that cannabis is implicated as the causative agent for all the categories, but on the contrary, research has shown that it may not only act as a causative agent, but may also worsen the pre-existing mental illness or may unmask the mental illness in predisposed subjects. Johns (2001) has accordingly divided the untoward mental effects of cannabis in three broad categories i.e. psychological responses (panic, depression, psychosis) related to excess consumption of the drug, effect of cannabis on pre-existing mental illness, and dependency or withdrawal effects. In this article we will use the standard nosological categories to describe the various effects of cannabis and wherever required will refer to the Johns system of classification.

## **CANNABIS USE DISORDERS**

### **Cannabis intoxication**

It is one of the least controversial issues in the research related to cannabis and have been divided into severe cannabis intoxication and pathological cannabis intoxication. Details of the clinical picture have been described in the previous review (Basu et al., 1994). Recent research has shown that the duration of intoxication would be longer in persons with previous history of schizophrenia or personality disorder (Johns, 2001).

### **Cannabis withdrawal syndrome**

Early clinic-based reports of cannabis abstinence syndrome were non-conclusive. Recently a number of clinical and community-based studies have examined this issue, targeting various elements of withdrawal syndrome such as onset, duration, and offset of symptoms; symptom pattern or presentation; and alternative explanations.

The studies reporting the onset and abatement of symptoms are very few, and the little available data are inconsistent. Earlier studies (Jones et al., 1976) reported symptoms starting at 4 hours and returning to baseline at 4 days, but the recent studies have reported a peak at 4-7 days (Haney et al., 1999; Kouri et al., 1999). A recent study on 18 outpatient cannabis users found that onset typically occurred between days 1-3 and peak effects between days 2-6, and most effects lasted 4-14 days (Budney et al., 2003). The remainder of the main withdrawal studies (e.g., Wiesbeck et al., 1996) makes no mention of time scale. Further, onset of withdrawal symptoms at 4 hours and lasting for a week

is not supported by the pharmacokinetic properties of cannabinoids such as long half-life and multiple bioactive metabolites (Grotenhermen, 2004).

Offset of symptoms, the cessation of symptoms on reintroduction of cannabis, has received limited attention with contradictory findings. In contrast to earlier anecdotal reports (Jones et al., 1976), a DSM-IV field trial (Cottler et al., 1995) found that reintroduction of cannabis could relieve such symptoms only in 11% of individuals, although these lower rates could be due to the use of dependent and nondependent users. However, in a recent well-designed laboratory study, it was found that oral tetrahydrocannabinol and not divalproex reduced the symptoms of putative cannabis withdrawal (Haney et al., 2004).

Regarding the withdrawal symptoms, early outpatient and laboratory studies reported sleep reduction or various other sleep problems, restlessness, irritability, sweating and chills, decreased appetite or change in appetite (Jones et al., 1976). Some of the recent studies have also confirmed the existence of similar symptoms (Wiesbeck et al., 1996; Budney et al., 1999; Haney et al., 1999). Additionally, studies that have looked for withdrawal symptoms with oral preparations have found stomach pain as one of the symptoms, which is not seen with smoked preparations (Haney et al., 1999). Autonomic symptoms have not been reported reliably. However, the specificity of these symptoms is again questionable. Studies which have examined the symptomatology in individuals who become dependent on non-substance behaviours, such as gambling, also reveal a cluster of symptoms centered around anxiety and irritability upon ceasing these behaviours (Gilbert et al., 1998) and absence of autonomic symptoms, similar to that of cannabis and due to the same withdrawal states in cannabis are questionable in not being distinct from general anxiety reaction.

The prevalence of these withdrawal symptoms again has wide variation ranging from 14% to 85% in the recent studies (Wiesbeck et al., 1996; Budney et al., 1999; Cottler et al., 1995), depending on the type of measurement used (self report/structured standardized tools), sample size, type of sample (cannabis users/ cannabis dependent subjects), amount of cannabis used and mode of cannabis use. Studies that have used standardized clinical instruments to measure severity reveal mild symptoms pattern (Kouri et al., 1999).

Most of the withdrawal studies have made some form of psychiatric evaluation prior to selection of the samples and have found various psychiatric disorders ranging from 41%

to 79% (Budney et al., 1999; Stephens et al., 1993). The only controlled study using standardized instrument to omit participants with psychiatric disorders found no withdrawal symptoms (Greenberg et al., 1976).

Further, many studies have limitations in the form of lack of operational definition for withdrawal symptoms, lack of control group, use of cannabis of poorer strength, use of oral forms rather than smoked form, and lack of blindness because most studies have used self administration.

From the above, it can be concluded that because of lack of severity of symptoms, the inconsistent onset and offset of such symptoms and the possibility of alternative explanations such as comorbidity, there is no unequivocal support for cannabis withdrawal syndrome under current definitions. In future, more rigorous research is required with a preset criteria for withdrawal syndrome and then measured with use of control participants, measuring the plasma levels of the drugs and correlating the same with the withdrawal symptoms. Recently published good-quality research under controlled conditions can shed more light on this currently 'hot' topic (e.g., Haney et al., 2004).

## **CANNABIS AND PSYCHOSIS**

### **Cannabis Psychosis**

One of the most heated debates in cannabis research concerns the existence of a distinct nosological entity that could be rightfully identified as cannabis psychosis. Earlier evidence of existence of this entity came from case reports (for details see Basu et al., 1994). The authors of these case reports attributed the psychosis to cannabis use for combination 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 psychosis 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 started using cannabis.

A number of controlled studies have been conducted over the past 25 years. Some case-control studies have either compared persons with "cannabis psychosis" with persons who have schizophrenia (Imade & Ebie, 1991; Thornicroft et al., 1992; McGuire et al., 1995; Basu et al., 1999) or

compared psychosis occurring in persons who do and do not have biochemical evidence of cannabis use prior to presenting for treatment (Chaudry et al., 1991; Mathers et al., 1991; Tien & Anthony, 1990; Thomas, 1996). Their results have been mixed. Studies in favour of a distinct entity have shown the cannabis psychosis to be short-lasting, presenting with a predominantly polymorphic clinical picture, presence of more odd and bizarre behaviour, violence, panic, but reactive and congruent affect, less evidence of schizophrenic formal thought disorder, and swift complete recovery compared to schizophrenia (Basu et al., 1999). The negative studies report that there are no differences in sociodemographic picture and symptoms that are unique to cannabis psychosis, and none that enabled them to distinguish a 'cannabis psychosis' from schizophrenia (Thornicroft et al., 1992).

The entity has been criticized by various authors (Thornicroft, 1990; Gruber & Pope 1994; Poole & Brabbins 1996; Schuckit, 1994) for 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 emphasize the wide variety of clinical pictures of "cannabis psychoses" reported by different observers of the case reports and case series.

Overall, it can be concluded that 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/ treatment/ evaluation. 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" (Poole & Braddins, 1996). It is plausible that high doses of cannabis may produce psychotic symptoms but the evidence for a specific clinical syndrome that is identifiable as a cannabis psychosis is much less compelling.

### **Cannabis and schizophrenia**

Clinical research has shown that high proportions of persons with schizophrenia report regular cannabis use and meet criteria for cannabis use disorders (Fowler et al., 1998; Mueser et al., 1990; Ziedonis and Trudeau, 1997). Epidemiological studies have also found an association between cannabis use and psychosis in the general population (Anthony & Helzer, 1991; Cuffel et al., 1993; Degenhardt & Hall, 2001; Tien & Anthony, 1990). There

has been considerable debate about the reasons for this association (Batel, 2000; Blanchard et al., 2000; Gruber & Pope, 1994; Hall, 1998; Hall & Degenhardt, 2000; McKay & Tennant, 2000; Mueser et al., 1998; Rosenthal, 1998). Depending upon the nature of the relationship between cannabis use and psychosis, four hypotheses have been proposed to explain the association. These are: cannabis use causes psychosis, cannabis use precipitates psychosis among vulnerable individuals, cannabis use worsens the prognosis of persons with schizophrenia and regular cannabis use is more likely among persons with psychosis.

According to the first hypothesis there is a causal link between cannabis use and schizophrenia in the sense that cannabis use causes cases of the disorder that would not have otherwise occurred. This hypothesis has arisen from reports of 'cannabis psychoses'. This hypothesis predicts that the age of onset of schizophrenia would decline in recent birth cohorts because of the age of cannabis initiation has declined, rising prevalence of cannabis use among persons with schizophrenia, an increase in incidence of schizophrenia because of increase in cannabis use among young adults and ultimately an increase in prevalence of schizophrenia. Studies have shown that subjects with first-episode schizophrenia who use cannabis are younger than those who do not (Linszen et al., 1994; Mathers et al., 1991; Rolfe et al., 1993), which supports this hypothesis. But there have been contradictory findings regarding the change in the incidence of schizophrenia. Numerous studies conducted in many countries have reported declines in the incidence of schizophrenia over the past 30 years (Geddes et al., 1993; Kendell et al., 1993; Munk-Jorgensen, 1995; Suvisaari et al., 1999). However, this has not been universal, with some reporting stable or increased rates (Bamrah et al., 1992; Harrison et al., 1991). Given uncertainty about whether there has been a decrease in incidence, the most conservative conclusion is that the incidence rates of schizophrenia have remained stable and possibly decreased over the past several decades.

According to the second hypothesis, regular cannabis use precipitates schizophrenia among vulnerable individuals, that is, among persons who would have developed the disorder regardless of whether they used cannabis or not (Hall, 1998). According to this hypothesis, an increase in regular cannabis use in the general population would not affect the incidence of schizophrenia but it would reduce the age of onset of psychotic illness among those who used cannabis. That is, the incidence rates of persons using cannabis would be 'brought forward'. If this led to more chronic psychotic disorders (e.g. because earlier onset cases are more likely to relapse), the prevalence of chronic cases of psychosis

would increase. This would increase the prevalence of regular cannabis use among persons with schizophrenia. The most convincing evidence that cannabis use may precipitate schizophrenia came from a 15-year prospective study of cannabis use and schizophrenia in 50,465 Swedish conscripts (Andreasson et al., 1988). 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, and the authors after controlling for the confounding variables concluded that cannabis use precipitates schizophrenia in vulnerable individuals. They also found a dose-response relationship between a diagnosis of schizophrenia and the number of times that cannabis had been used by age 18. In a recent follow-up of the same cohort it has been concluded that heavy cannabis users by the age of 18 years were 6.7 times more likely than non-users to be diagnosed with schizophrenia 27 years later (Zammit et al., 2002); and the risk remained significant after controlling for other potential confounding factors such as disturbed behaviour, low IQ score, growing up in a city, cigarette smoking and poor social integration. Similar increases in risk of development of schizophrenia after cannabis use have also been reported by other epidemiological follow-up studies ranging from 3 years to more than 20 years (Fergusson et al., 2003; van Os et al., 2002) and have also found evidence for the presence of dose-response relationship (van Os et al., 2002). Other supporting evidence for this hypothesis is that persons with first-episode schizophrenia who use cannabis are younger than those who do not (Linszen et al., 1994; Mathers et al., 1991; Rolfe et al., 1993); cannabis use usually precedes the development of psychotic symptoms (Allebeck et al., 1993; Hambrecht and Haefner, 2000; Linszen et al., 1994); among first-episode cases of psychosis, those who used cannabis were more likely to have a family history of psychosis (McGuire et al., 1995; Boutros & Bowers, 1996); their better premorbid adjustment, their fewer negative symptoms, and their better treatment response. This hypothesis is also consistent with the stress-diathesis model of schizophrenia (Boutros & Bowers, 1996; Gottesman, 1991) in which the likelihood of developing schizophrenia is the product of stress acting upon a genetic diathesis to develop schizophrenia.

According to the third hypothesis, cannabis use would worsen the prognosis of schizophrenic persons by increasing relapse to schizophrenia. This hypothesis does not predict an increased incidence of schizophrenia among regular cannabis users. Instead, it predicts that persons with schizophrenia who are regular cannabis users will be more likely to have a relapse after their initial episode. This could increase the number of persons in the population with

chronic schizophrenia. It would not affect the age of onset of psychosis. The prevalence of cannabis use among persons with schizophrenia would increase because there would be more cannabis users among chronic cases. It is supported by evidence that persons with schizophrenia who use cannabis are more likely to suffer a relapse (Jablensky et al., 1992; Linszen et al., 1994; Negrete et al., 1986) and stable incidence of schizophrenia as discussed above. 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 (Stahl, 1996). Cannabinoids, such as THC increase dopamine release (Hamara et al., 1995). 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 (Kavanagh, 1995). The other difficulty is about separating the contributions that cannabis and alcohol make to exacerbations of schizophrenic symptoms. It is rare for a schizophrenic patient to only use cannabis (Mueser et al., 1992). The concurrent use of alcohol is common, and the heavier their cannabis use, the more likely they are to use psychostimulants and hallucinogens. The only study [Linszen et al. (1994)] statistically adjusted for the effects of concurrent alcohol and drug use and found that the relationship persisted.

According to the fourth hypothesis, persons with schizophrenia are more likely to become regular cannabis users, if they use the drug. There is no causal relationship between cannabis use and psychosis, so increasing rates of cannabis use will have no effect upon the incidence or prevalence of schizophrenia and there would not be a change in age of onset. There would be an increased prevalence of cannabis use among persons with psychosis. Findings in favour of the hypothesis is the evidence that some schizophrenic patients report using cannabis because its euphoric effects relieve negative symptoms and depression (Dixon et al., 1990). Dixon et al. (1990) 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.

Although recent, double-blinded, randomized, counterbalanced laboratory studies have clearly demonstrated the psychotomimetic properties of intravenous tetrahydrocannabinol (D'souza et al., 2004), these cannot answer the question: what happens to people *long-time*

*after* they have been using cannabis? Prospective cohort studies can possibly answer this question. Two recent publications (Arseneault et al., 2004; Smit et al., 2004) have reviewed the few original high-quality longitudinal cohort studies available in this area from four countries: Sweden (Andreasson et al., 1988; Zammit et al., 2002); Israel (Weiser et al., 2002); Netherlands (van Os et al., 2002); and New Zealand (Arseneault et al., 2002; Fergusson et al., 2003). The follow-up period varied from 3 – 15 years across studies. Outcome was defined differently, varying from a count of number of psychotic symptoms to full-fledged ICD or DSM-defined schizophrenia or schizophreniform disorder. All these studies had eliminated effect of prior history of psychosis, and most (other than Weiser et al., 2002) had eliminated the effect of other substances. Except one (Arseneault et al., 2002), all studies had controlled for the possible confounding effects of several sociodemographic and clinical variables such as gender, age, ethnicity, marital status, education, employment, IQ, social network, urbanicity, etc. Based on these, both the reviewers concluded that cannabis use in adolescence leads to at least a twofold increase in the relative risk of schizophrenia or related psychoses in adulthood (adjusted pooled Odds ratio = 2.34; 95% CI = 1.69 - 2.95). Although confounding effects cannot be totally eliminated, the overall evidence suggests cannabis was more harmful in vulnerable subjects, i.e., those 'at risk' for developing psychotic illnesses by virtue of family history or adverse past history. Cannabis did not appear to represent a sufficient or a necessary cause for the development of psychosis but forms parts of a causal constellation. Although the risk of developing psychotic disorders was numerically small, this minority was significant from both the clinical point of view and at the population level. Arseneault et al. (2004) even estimated that about 8% of schizophrenia could be prevented by elimination of cannabis use in the population.

From the above review it can be concluded that cannabis use might be causally related to development of schizophrenia in an indirect way, but its use may precipitate disorders in persons who are vulnerable to developing psychosis and worsen the course of the disorder among those who have already developed it.

## CANNABIS AND AFFECT

### Depression

The association between cannabis and depression has received much less attention than potential links between cannabis use and psychosis, probably because of depressed

cannabis users seeking much less treatment and underreporting of cannabis use by depressed patients because of its illegal status.

Findings from the convenient community sample have provided conflicting evidence on the association between cannabis use and depression. Studies have shown that life time use of cannabis increases the risk of depression in females (Rowe et al., 1995), leads to greater suicidal ideations (Field et al., 2001), increases the level of depression with increasing involvement with cannabis use (Troisi et al., 1998; Milich et al., 2000). On the contrary, no difference was found between light and heavy users in the number of depressive symptoms reported (Musty and Kaback, 1995), depression and suicidal ideations (Galaif et al., 1998). However, the above findings cannot be generalized because of small sample size (Kouri et al., 1995), use of specific populations like college students (Kouri et al., 1995), young adult males (Green & Ritter, 2000), army draftees (Troisi, 1998), and lack of comparative groups (Troisi, 1998; Kouri et al., 1995).

Studies from general population are more forthcoming about the association between depression and cannabis use. The Epidemiologic Catchment Area (ECA) and the National Comorbidity Survey (NCS) reported association between drug use disorders (which included cannabis and other substance use disorders) and depression. Chen et al. (2002) reanalyzed the NCS data with a specific focus on cannabis use and major depressive disorder and found that greater number of occasions of cannabis use were associated with a higher risk of having experienced a major depressive episode and that life time DSM III R cannabis dependence was associated with a 3.4 times increased risk of major depression. In another epidemiological study Grant et al. (1995) found that people meeting criteria for DSM IV cannabis abuse or dependence within the past year had 6.4 times the odds of meeting criteria for DSM IV major depression than those who did not meet criteria for drug abuse/dependence. Degenhardt et al. (2001) examined the relationship between different levels of cannabis use (no use, use, abuse or dependence) and depression in the Australian National Survey of Mental Health and found that those who were more heavily involved with cannabis use were more likely to meet criteria for DSM-IV mood disorders. Similar findings have been reported from adolescent population using cannabis (Rey et al., 2002). Fergusson et al. (2003) found that adolescents who had used cannabis 10 or more times by the age of 15-16 years were more likely to also meet criteria for a mood disorder

at that age. A study of Patton et al. (2002) using a representative cohort of young adults (aged 20-21 years) in Victoria found that 68% of females who reported daily cannabis use in the past year were depressed - an odds ratio of 8.6 compared to non-users. Brook et al. (1998) in a 10-year follow up study of students aged 12-14 years found that, reporting lifetime cannabis use had higher depression scores, and 42% met criteria for DSM-IV major depression at some point in their lives.

To summarize, there is increasing recent evidence that regular cannabis use and depression occurs together more often than we might expect by chance. While not all studies have found a significant association, the weight of evidence indicate that there is an increased chance of depression among people who report heavy or problematic cannabis use. The strength of the association is, however, only modest, especially after controlling for potential confounding variables; hence, it is still too early to rule out the hypothesis that the association is due to common social, family and contextual factors that increase risks of both heavy cannabis use and depression (Degenhardt et al., 2003).

Accordingly, it is important to try to understand the basis of this association between cannabis and depression. Three hypothesis or possible theories of association are cannabis use may be a contributory cause of depression; depression may be a contributory cause of cannabis use and there is no direct relationship between the two, with the observed association explained by shared risk factors that increase the risk of both disorders. Various cross-sectional and longitudinal studies have examined the association and have provided mixed evidence on the nature of the association between cannabis use and depression. Cross-sectional studies (Degenhardt et al., 2001; Rowe et al., 1995; Green et al., 2000; Rey et al., 2002) have suggested that the relationship can be explained by other factors such as the use of other drugs. Longitudinal studies (Bovasso, 2001; Merikangas & Angst, 1995; McGee et al., 2000) have consistently indicated that the 'self-medication' hypothesis does not fit the pattern of cannabis use over time among cohorts of adolescents and young adults. There is more mixed evidence that heavy cannabis use increases the risk of depression during follow-up, and this relationship is partly but not completely explained by confounding variables. A recent study by Sullivan et al. (2000) suggested that the association between depression and cannabis dependence may be explained partially by a high degree of overlap in genetic factors predisposing to cannabis use and depressive disorders, lending support to the hypothesis of shared risk factors.

## Mania

Strakowski et al. (1996) reported that among the various drugs of abuse, cannabis was more commonly associated with mania, but the cannabis use did not affect the age of onset of bipolar disorders. In a later study they showed that duration of cannabis abuse was positively correlated with duration of mania in new-onset bipolar disorder cases (Strakowski et al., 2000). A recent study from India (Sarkar et al., 2003) found that of the 244 patients with cannabis-related diagnosis attending their centre, 12% received a diagnosis of bipolar disorder – mania with psychosis, the third common psychiatric condition after cannabis-induced psychosis (21%) and schizophrenia (14%). Even the commonest presentation of cannabis-induced psychosis in their series was that of predominantly manic type. It is possible that acute psychotic agitation with mania brings the condition to early treatment attention. Interestingly, cannabis has been anecdotally suggested to have mood-stabilizing property in bipolar disorder (Grinspoon and Bakalar, 1998), though no such studies are available.

## Panic and anxiety

Anxiety is probably the commonest adverse reactions with cannabis use, but most cases do not seek medical attention and resolve spontaneously. Panic attacks constitute the most frequent acute anxiety syndrome associated with cannabis use (Thomas, 1993; Hall and Solowij, 1998), and 20–30% of consumers present with acute and brief anxiety reactions after smoking cannabis (Thomas, 1996). Other studies have suggested that cannabis use may be associated with long-lasting anxious symptomatology. In a study of persons who regularly used cannabis for at least 10 years, Reilly et al. (1998) found that 21% of these subjects had high levels of state anxiety, and several case reports have described cannabis-induced agoraphobia (Moran, 1986) and panic disorder (Deas et al., 2000; Langs et al., 1997). A speculative hypothesis regarding the association of cannabis use and agoraphobia concerns the emergence of anticipatory anxiety secondary to previous cannabis induced panic-like symptoms. Few epidemiological investigations have examined the comorbidity of anxiety disorders and cannabis use in the general population. Using data from the Australian National Survey of Mental Health and Well-Being, Degenhardt et al. (2001) have reported an association between cannabis use over the past year and increased prevalence of anxiety disorders. Among individuals with cannabis dependence, 17% had at least one anxiety disorder compared to 5% of non-users. However, this association disappeared after adjustment for demographic

characteristics, personality disorder and use of others drugs. Although these studies suggest that an association may exist between cannabis use and high levels of trait or state anxiety, they are not informative concerning the direction of this association (Compton et al., 2000; McGee et al., 2000; Mueser et al., 1998). Thus, it is currently unclear if anxiety is best conceptualized as a consequence of cannabis use in vulnerable subjects, or conversely, if anxiety disorders may favour cannabis use. An additional possibility is that both cannabis use and anxiety disorders may be independently induced by a shared risk factor, such as specific pre-existing personality traits. Tournier et al. (2003) examined the association of cannabis and anxiety and found that a diagnosis of agoraphobia was significantly associated with increased likelihood of cannabis use, independent of state anxiety and other confounding factors. No evidence was found for an anxiolytic or anxiogenic effect of cannabis in daily life. This finding does not support the hypothesis that subjects with high levels of anxiety use cannabis as a means of self-medication. The association between agoraphobia and cannabis use in daily life may be explained by anticipatory anxiety secondary to previous cannabis-induced panic-like symptoms. Importantly, cannabis-precipitated panic disorder (both with or without agoraphobia) has been shown to be as responsive to treatment with paroxetine as panic disorder not associated with cannabis in a recent study (Dannon et al., 2004).

## CANNABIS AND OTHER PSYCHOPATHOLOGY

### Amotivational syndrome

This presumed psychological syndrome is believed to be a direct result of regular, heavy cannabis use and leaves those so affected reduced in motivation and capacity for the usual activities required for achievement and success in today's world. Although many anti-cannabis campaigners accept, *a priori*, the existence of the 'amotivational syndrome', there is considerable doubt as to whether it is an actual nosological entity and whether all cannabis users are so affected. Some authors do not consider it to be a single nosological entity but rather a change in cognitive style emerging as a result of cannabis's ability to facilitate a unique attentional state favoured by those who have a higher than average level of a personality factor referred to as 'trait absorption'. Exaggeration of the absorptive style of cognition through cannabis use, when taken in the context of either a pre-existing or a reactive depression, may be what has been mistakenly categorized as 'amotivational syndrome' (Nelson et al., 1993)

## Echo or Flashback phenomenon

First reported by Keeler et al. (1968), these consist of re-experiencing the various perceptual and cognitive effects of the drug at a later date while not under its influence any more. Although better known with hallucinogens, several reports of cannabis flashback have also been published (for details see Basu et al., 1994).

The newer understanding of the pharmacokinetics of cannabinoids puts in doubt the existence of truly drug-less flashback reactions. It seems quite possible that such experiences may be the result of a continuous or intermittent release of psychoactive component from adipose tissues where they are stored during periods of active usage (Thomas, 1993). According to the available data they occur rarely and require a thorough differential diagnostic evaluation in each individual case, especially to rule out concomitant hallucinogen consumption (Fischer & Taschner, 1991). A recent interesting case report from Switzerland described a young man who offended a friend without any objective reason. The report of the forensic psychiatrist demonstrated that the offense was committed under the influence of a cannabis flashback, proven subsequently by laboratory detection of cannabinoids in plasma during another flashback, thus highlighting the medicolegal implications of the phenomenon (Niveau, 2002).

## Cognitive impairments

The cognitive effects of long-term cannabis use and their implications are insufficiently understood (Malhotra & Basu, 1997). In contrast to the heated polarization that characterized this debate, most well-designed studies concur that modest cognitive deficits occur with heavy and prolonged use of cannabis and persist at least several weeks after stopping heavy cannabis use. The most consistent findings are impairment of performance on tests of focused attention, short-term memory, perceptuomotor functions, and 'executive functions' such as set-shifting (Block and Ghoneim, 1993; Fletcher et al., 1996; Solowij et al., 1995; Pope & Yurgelun-Todd, 1996; Ehrenreich et al., 1999). Solowij et al. (1995) further assessed the persistence of the cognitive deficits after stopping cannabis and found partial recovery of function but the past duration of cannabis use continued to have an adverse effect on the ability to effectively reject complex irrelevant information. There was no indication of improvement with increasing length of abstinence. It must, however, also be noted that the impairment in these areas are mostly modest in magnitude, often just reaching statistical significance. Their clinical

significance remains uncertain (Kouri et al., 1995; Pope & Yurgelun-Todd, 1996).

## Conclusion

What has changed in the last 10 years regarding cannabis and psychopathology? It may depend upon how one looks at the field. Stoics may not see a sea change in our knowledge in this area. However, considering the very substantive difficulties and challenges involved in clinical research with cannabis (Basu et al., 1994), it is remarkable that such a substantial volume of reasonably well-designed research has taken place in the last decade. An important area of stride has been the extending the locus of studies from purely clinic-based and laboratory-based to the large, community-based epidemiological studies conducted in the 1990s. This has helped us to confirm, refute or modify the hypotheses formed from the clinic-based studies in many cases. Another important area opened up during the last decade is the establishment of an association between cannabis use and non-psychotic psychopathology, predominantly depression and anxiety. The nature of this association, however, remains speculative. The need for further research in this important area has been demonstrated in a convincing manner. Mild residual cognitive impairment resulting from chronic cannabis use has also been demonstrated, although its clinical significance remains to be demonstrated. The evidence and informed opinion regarding cannabis withdrawal and the putative 'cannabis psychosis' seems to weigh against the latter at least. Regarding the established association between cannabis and schizophrenia, the research during the last decade has shown that cannabis use might be causally related to the later development of schizophrenia in an indirect way in a few heavy users, but its use may precipitate disorders in persons who are vulnerable to developing psychosis and worsen the course of the disorder among those who have already developed it. All these have clear-cut academic as well as purely pragmatic implications. The future decade should, hopefully, be able to throw new light on this important area. Considering the fact that India remains a traditional cannabis use country, the importance of research from our country cannot be overestimated.

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## Sandeep Grover & Debasish Basu

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