

CANNABIS RELATED PSYCHIATRIC SYNDROMES: A SELECTIVE REVIEW

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Association between cannabis use and various psychiatric syndromes does exist, but their nature remains elusive. Cannabis intoxication, 'cannabis psychosis' and certain other conditions related with cannabis use like flashbacks and prolonged depersonalization are discussed in this paper. The controversial nature of the cannabis - schizophrenia link is noted, and various methodological issues in clinical cannabis research are highlighted.

Key words: Cannabis, cannabinoids, marijuana abuse, psychopathology, psychosis.

INTRODUCTION

Used in the Vedic era in India (Andrews & Vinkenoog, 1967) and recently identified in Egyptian and Peruvian mummies (Parsche et al, 1993), cannabis is certainly not a new drug. Basic biological research in cannabis and its psychoactive components - the cannabinoids (Mechoulam, 1970) has made great strides in the past 30 years, from isolation of delta-9-tetrahydrocannabinol or simply THC (Gaoni & Mechoulam, 1964), to molecular characterization and anatomical localization of cannabinoid receptors in the brain (Matsuda et al, 1990; Herkenham et al, 1990) as well as in peripheral tissues (Munro et al, 1993). The latest excitement surrounds the discovery of an endogenous ligand for the cannabinoid receptor, named 'anandamide' from the Sanskrit word 'ananda' or bliss (Devane et al, 1992).

Despite all these recent advances in the biomolecular research in cannabis, considerable controversy still rages around the clinical delineation of adverse psychological effects of cannabis or the cannabis related psychiatric syndromes (Negrete, 1988; Basu, 1992; Mathers & Ghodse, 1992; Thomas, 1993). This is in spite of the fact that psychiatric effects of cannabis have been documented for more than one and a half centuries now (O'Shaughnessy, 1838-40; Moreau de Tours, 1845). Cannabis is probably the only drug that has been the focus of more than half a dozen national level enquiries in different countries over the last century, e.g., India (Indian Hemp Drugs Commission of Inquiry into the Nonmedical use of Drug, 1972), etc. Any clear-out consensus is, however, yet to emerge. This provides the backdrop for this selective review and current status.

OFFICIAL NOSOLOGICAL SYSTEMS

The existing nosological uncertainty is reflected in both the official American (DSM III & III-R,

American Psychiatric Association 1980 and 1987, respectively) as well as International (ICD-9 & 10, World Health Organization, 1978 and 1992, respectively) classification systems. In the ensuing discussion, the variously described syndromes of abuse, harmful use, dependence and withdrawal will not be reviewed.

In both DSM-III and III-R, under the section heading 'substance induced organic mental disorders' there are two categories specifically concerned with cannabis: cannabis intoxication and cannabis delusional disorder. While there is no controversy regarding the former (with very minor changes in the revised edition), the texts explicitly state that the existence of the latter category is controversial. It required the following criteria to be fulfilled in DSM III: A. Recent use of cannabis; B. An organic delusional syndrome within two hours of cannabis use; C. Duration of the syndrome not more than six hours following cessation of use; D. Not due to any other disorder. In DSM III-R, however, the duration criterion was dropped, and onset of the syndrome after cannabis use was relaxed from 'two hours' to 'shortly'.

While the American system was striving to be specific, the International system was broad and non-specific. The ICD-9 accommodated cannabis and other drugs (drug-induced psychosis with paranoid/hallucinatory features: code 292) and even other etiological factors (transient organic psychotic state: code 293). Further details related to cannabis were not provided.

ICD-10

This takes a much wider approach. Nine groups of psychoactive substances are covered under the heading F1: Mental and Behavioral disorders due to Psychoactive substance use, the 'Disorders resulting from use of cannabinoids' featuring as code F 12. Each of these 9 classes of substances may potentially

produce 10 types of clinical conditions, to be coded as 4th and 5th character codes. These include: 1) acute intoxication, 2) harmful use, 3) dependence syndrome, 4) withdrawal state, 5) withdrawal state with delirium, 6) psychotic disorder, 7) amnesic syndrome, 8) residual and late-onset psychotic disorder, 9) others, and 10) unspecified clinical conditions.

Many of these again have multiple sub-categories. The approach has the empirical advantage of retaining more information than DSM III-R approach of specifying clinical conditions due to particular groups of drugs. For example, an acute-onset psychosis after recent use of cannabis with predominantly polymorphic picture cannot be satisfactorily coded in DSM III-R, but in ICD-10 this will be coded as F12.53, i.e., Disorders resulting from use of cannabinoids, psychotic disorder, predominantly polymorphic. However, the disadvantage of this approach is that while ensuring a broader coverage of syndromes, specificity is lost - any substance can potentially produce almost any psychiatric disorder. In summary, the DSM approach is more specific but not exhaustive, whereas the ICD approach is more exhaustive but with a compromise on specificity. This nosological issue is still far from satisfactory.

With this background, let us examine a widely used 'classification' of cannabis related psychiatric syndromes (Negrete, 1973). This teases out certain specific psychiatric conditions out of the various adverse psychological effects of cannabis, in terms of symptomatology, pattern of cannabis use, and duration of the illness. These are:

1. Severe cannabis intoxication
2. Pathological cannabis intoxication
3. Acute cannabis psychosis
4. Subacute and chronic cannabis psychosis
5. Residual conditions such as amotivational syndrome, "echo" or "flashback" phenomenon, and persistent depersonalization.

THE INTOXICATION SYNDROMES

Severe cannabis intoxication:

There is probably the least controversy here (Tart, 1970; Weil, 1970). After consuming a large quantity of cannabis, the usual pleasurable effects of cannabis may be intensified to the extent of being unpleasant. In addition, one may have clouding of consciousness, disorientation, depersonalization

and derealization, paranoid ideation, gross sensory distortion and deception in any sensory modality including visual and auditory hallucinations and transient cerebellar or pyramidal / extrapyramidal signs. Here the onset is sudden, closely following the cannabis consumption (faster when smoked), and duration is only a few hours. It is a dose related phenomenon, though the exact intensity and duration of the symptoms would depend upon characteristics of the agent (i.e., the cannabis preparation and its potency), the host (e.g., the mental set of the subject and his past experiences with cannabis) and the environment (i.e., the setting in which cannabis is taken). Many symptoms have recently been explained on the basis of cannabinoid receptor localization patterns in the brain (Herkenham et al, 1990).

Pathological intoxication:

This has a similar clinical picture; the onset and duration being similar to that of severe cannabis intoxication, except for the fact that it is precipitated by an average, usual or low dose of cannabis. These terms qualify with reference to the particular user in question. States are also more often characterized by panic attacks, persecutory ideation, or acute depressive reaction. The affective component in the clinical picture is usually more prominent than the cognitive component. According to Negrete (1973), personality factors, expectations and setting play important roles in the genesis of this disorder. However, because of operational difficulties in deciding between a 'large' and a 'small' dose, it is generally not a nosological category, except in ICD-10 where it appears as a fifth character subcategory under 'acute intoxication' (F 12.07) and then "applies only to alcohol". not cannabis (WHO, 1992).

THE "CANNABIS PSYCHOSIS" SYNDROMES

One of the most heated arguments in the recent ongoing cannabis debated concerns the existence of a distinct nosologic entity which could be rightfully identified as 'cannabis psychosis'. Although alluded to in the Indian Hemp Drugs Commission Report in 1893-94, the first scientific communication regarding the 'Indian Hemp Insanity' came from Ewens in 1904. In fact, this condition was earlier thought to be "peculiar to the country", i.e., India (Dhunjibhoy, 1930). Though later reported from various parts of the world, such as India (Varma, 1972; Thacore, 1973; Chopra & Smith, 1974; Thacore & Shukla, 1976; Chaudhury & Augustine, 1989) Pakistan (Chaudhry et al, 1991), African countries (Rottan-

burg et al, 1982; Solomons et al, 1989; Imade & Ebie, 1991), Scandinavian countries (Bernhardson & Gunne, 1972; Palsson et al, 1982; Tunving, 1985), West Indies (Knight, 1976), the United Kingdom (Carney et al, 1984; Drummond, 1986; Onyango, 1986) and the United States of America (Kolansky & Moore, 1971), the clinical validity and nosologic status of these cannabis psychoses syndromes remain unclear.

Ghodes (1986) reviewed this area recently and arrived at the conclusion that it is quite certain that cannabis is capable of causing an acute toxic psychosis with confusion, disorientation, delusions, hallucinations and affective symptoms. This seems to be dose-related, with a predictably brief and self-limiting course of hours of hours to a few days after cannabis use is stopped.

The evidence for a longer-lasting "functional psychosis" is rather weak, though not entirely ruled out. This category, characterized by paranoid, hallucinatory and / or hypomanic features with relatively clear sensorium, appearing in long-term heavy cannabis users and lasting for weeks to months, has been subject to the greatest controversy (Negrete, 1988). An alternative view is that the basic disorder is an independent functional psychosis, especially schizophrenia or affective disorder, which is precipitated, aggravated or modified by the use of cannabis; this view seems to be favored currently (Mathers & Ghodes, 1992; Thomas, 1993b; Saxena, 1993). However, protagonists of the "functional cannabis psychosis" maintain that this is an independent nosological entity in its own right. They support their argument by the following facts: these patients usually do not have evidence for latent or overt psychosis prior to the cannabis use, 2) some clinical features tend to differentiate the two groups of cannabis psychosis and schizophrenia or affective disorder, 3) the psychotic illness almost invariably subsides after stoppage of cannabis use, 4) often there is a psychotic relapse when cannabis use is resumed, and finally, 5) cannabinoids and their active metabolites may indeed last in the body for a month or more, documented by sophisticated laboratory techniques (Bernhardson & Gunne, 1972; Tunving, 1985; Drummond, 1986; Onyango, 1986).

In India, a recently conducted clinical survey found non-specific psychosis and persecutory delusions in nearly half of 170 patient of cannabis abuse attending a deaddiction clinic and that "the cross-sectional profile of psychiatric morbidity ap-

peared to be different from schizophrenia and affective disorders" (Ramachandran et al, 1989). A case control study done by us (unpublished) on the clinical features, course and outcome of "cannabis psychosis" vis-a-vis acute schizophrenic episode also warrants similar conclusions. The issue however, is far from settled because of the many methodological problems (discussed later).

THE "AMOTIVATIONAL" SYNDROME

Described first by McGlothlin & West (1986), this is defined as "a set of symptoms including apathy, ineffectiveness and non-productiveness considered to reflect a deficit in general motivation... resulting from the use of certain drugs" (Commission of Inquiry into the Non-medical Use of Drugs, 1972). Many regular cannabis users were observed to become apathetic, lose drive and sense of purpose, indulge in idle day dreaming and evade activities which required sustained goal directed effort. After initial debate, with opposite views coming from different countries like Greece (Mellinger et al, 1976), India (Chopra & Jandu, 1976), Canada (Campbell, 1976) and West Indies (Comitas, 1976), it is generally held now that if cannabis users do differ from non-users with respect to the above mentioned features, the differences may simply arise from dissimilarities in their social, family and psychological backgrounds, and that such a state should not be thought of as a separate clinical entity (Granville-Grossman, 1979; Negrete, 1988).

OTHER PSYCHIATRIC SYNDROMES RELATED TO CANNABIS

Echo or Flashback phenomenon:

First reported by Keeler et al (1988), 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 LSD, several reports of cannabis flashback have also been published (Bialos, 1970; Stanton & Bardoni, 1972; Chopra & Smith, 1974; Keshavan & Lishman, 1986). 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). The flashbacks may be indeed pleasant to some users (Stanton et al, 1976).

Persistent depersonalization:

There are only a few case reports where cannabis use led to a state of prolonged depersonalization (Szymansky, 1981; Keshavan & Lishman, 1986). The mechanism is unclear at present, though it may again be related to the long elimination half-life of active cannabinoid metabolites, or may be due to residual neurotoxicity of cannabinoid products.

Cannabis and schizophrenia:

Both clinical (Schneier & Siris, 1987) as well as community (Bland et al, 1987) studies found the lifetime prevalence of cannabis use to be significantly higher among schizophrenics than in comparison groups, including other psychiatric disorders (Weller et al, 1988). Also, many schizophrenics seem to prefer cannabis to other drugs except tobacco (Knudsen & Vilma, 1984; Schneier & Siris, 1987). A doubled risk of psychotic experiences was found in daily users of marijuana in a large scale community survey (Tien & Anthony, 1990), though not universally agreed upon (Thornicroft, 1990). Finally, it is accepted that cannabis use alters schizophrenic course (Treffert, 1978), by either increasing positive symptoms (Negrete et al, 1986) or decreasing negative symptoms, especially alogia (Peralta & Cuesta, 1992).

The true nature of this apparent association between cannabis use and schizophrenia, however, remains controversial. Large scale register based Swedish studies indicate use (and especially heavy use) of cannabis to be an independent risk factor for later development of schizophrenia and not the other way round (Andreasson et al, 1987 & 1989; Allebeck et al, 1993). Although theoretically tenable by the property of cannabis to increase brain dopamine levels (Patel et al, 1985) or to amplify pre-existing trend of deviant behavior (Foltin et al, 1987), this view is not endorsed by others (Johnson et al, 1988; Negrete, 1989; Mathers & Ghodse, 1992), who consider that other confounding variables (e.g., other drug use, premorbid personality, background sociocultural and ethnic / environmental factors) have to be considered before drawing such a causal conclusion.

METHODOLOGICAL ISSUES IN CLINICAL CANNABIS RESEARCH

1) Cannabis is a pharmacologically "dirty" drug (Ashton, 1987). It contains so many active compounds, each with different pharmacokinetics and detectability, wherein it becomes very difficult to

study the effects of cannabis in relation to any one compound. Also, the concentrations of these vary from one cannabis preparation to another.

2) Cannabis is rarely taken in isolation. Quite often other drugs or alcohol are used concomitantly, agents that may be etiologically related to the target syndrome studied.

3) Lack of proper sampling often makes interpretation of studies difficult. Most samples are 'samples of convenience' rather than 'samples of choice'.

4) Earlier studies often did not employ a comparison group. Later studies, although employing various control groups, have often employed inappropriate controls. This has been a consistent limitation in many studies regarding amotivation syndrome, cannabis psychosis and cannabis induced organic brain damage.

5) Most studies are retrospective in design. Not that these are totally non-contributory, but the interpretation calls for caution.

6) Another methodological hurdle is the unreliability of reported drug use data, especially cannabis. Chances of retrospective falsification are high. Also, in India, people often use the terms 'ganja', 'bhang', 'charas', 'sulfa', and 'sukha' incorrectly and interchangeably. This makes quantification difficult.

7) Application of standardized instruments is another problem, especially in the study of cannabis psychosis. Since the form and content of psychopathology are often culturally influenced, proper choice of a psychopathology rating scale becomes important across cultures.

8) Inferences drawn from different theoretical frameworks differ themselves. Thus, researchers who consider schizophrenia to be the basic disorder and cannabis to influence its course, will study the role of cannabis in schizophrenia. Another group of researchers who incorporate the concept of an independent cannabis psychosis in their theoretical framework will probably consider the same data to infer that cannabis does cause cannabis psychosis. For example, the same study by Rottanburg et al (1982) has been cited by some authors to support the notion of 'functional cannabis psychosis' (Ghodse, 1988) and by other authors to show the influence of cannabis on schizophrenic symptomatology (Peralta & Guesta, 1992), whereas Rottanburg et al's original paper was simply on 'cannabis-associated psychosis with hypomanic features'.

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9) The pathoplastic influence of sociocultural factors is another important issue, especially in discussions on the amotivational syndrome and cannabis psychosis.

10) Finally, it has been commented that a truly 'unbiased' researcher in the cannabis issue is only rarely found. With cannabis, personal and social attitudes and norms often dominate in the interpretation of drug effects. For example, cannabis effects subjectively considered 'psychedelic' or 'peak' may be defined as 'psychotic' by others. Feelings of increased sensitivity to humor may be alternately viewed as 'loquacious euphoria' by others (Commission of Inquiry with the Non-medical use of Drugs, 1972).

CONCLUSION AND SUGGESTIONS FOR FURTHER RESEARCH

Are we much wiser than when we began? Considering the numerous methodological obstacles in research in the field, the answer is uncertain. This, of course, should not mean that further research in this area would be futile. Equipped with more sophisticated laboratory techniques, more sensually validated instruments, an ever increasing treasure of knowledge regarding the existence and delineation of certain cannabis related psychiatric syndromes, and finally, with the much more exhaustive list of cannabis related clinical conditions nosologically agreed to by the ICD-10, probably the time is set for much more scientific as well as culturally valid research in this area than ever before.

In India, a particular section of the lower socioeconomic strata has long been noted for regular, customary and heavy use of cannabis. This section is remarkable for the consistency of cannabis use, "consistency" being qualified not only in terms of chronicity and heaviness of use, but also in terms of use of a particular preparation (e.g., ganja or bhang), situation of use (e.g., in "social" gatherings in a temple), time of use (e.g., towards the evening after the day's work is over), and relative absence of other substance use (except tobacco and occasionally alcohol). This sizeable section of chronic heavy cannabis users has surprisingly evaded rigorous scientific attention so far. Carefully designed prospective longitudinal studies (preferably multi-centric) employing this section as a community cohort should yield very useful information about epidemiology, biopsychosocial aetiology, nosology, course and outcome of various cannabis related

psychiatric syndromes. This may indeed be a unique Indian contribution to the relevant world literature.

Given, however, the considerable practical difficulties inherent in conducting such community level studies, even clinic based prospective cohort studies may partly help. Though not very useful for epidemiology and aetiology, these may shed further light on other aspects, especially on the current issue of cannabis abuse and course of schizophrenia, as demonstrated by a recent well designed study from the Netherlands (Linszen et al, 1994) and another from Spain (Martinez-Arivalo, 1994). Both these studies showed that cannabis abuse was a specific risk factor for psychotic relapse over one year of prospective follow-up. Similar studies from India are feasible, potentially useful, hence warranted.

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