

Cannabis — its clinical effects

K. SOLOMONS, V. M. NEPPE

Summary

The range of clinical, intoxicating, psychological and psychiatric effects of cannabis ('dagga') are reviewed. Controversial subjects, such as the entities of toxic cannabis psychosis and the cannabis amotivational syndrome, are discussed.

S Afr Med J 1989; 76: 102-104.

Cannabis sativa ('dagga') affects the central nervous system (CNS) in a variety of ways although its biochemical modes of action are unknown. There is some evidence to suggest that Δ -9-tetra-hydrocannabinol (Δ -9-THC), the most psychically active constituent, effects serotonin metabolism in the brain by increasing serotonin release from reserpine-sensitised sites by causing a shift from the bound to the free intraneuronal pool of serotonin and by causing an increased rate of serotonin synthesis from serotonin precursors.¹⁻³

There is also evidence to suggest that cannabinoids interact with other psycho-active drugs and can potentiate the effects of alcohol, caffeine, amphetamines and barbiturates in man.^{4,5} This phenomenon could be a potentiation in the CNS but in

non-chronic users of cannabis is more probably mediated by the microsomal oxidase enzyme system in the liver.

Clinical effects

The typical immediate physical effects of cannabis use include dry mouth and throat, tachycardia, postural hypotension, conjunctival vessel injection that causes red eyes and leaves the pupils unaffected, and mild initial bronchoconstriction followed by bronchodilation. Tachycardia is probably the most reliable index of physiological response to cannabis.⁶⁻⁸

The major intoxication effects of cannabis include mood elevation and a feeling of well-being and perceptual and sensory distortions. Both external senses and internal stimuli are enhanced and experienced as more intense and meaningful. Time and distance perception are distorted. Libido and appetite may be enhanced and short-term memory and judgement may be impaired. These effects usually last for up to 8 hours.⁹⁻¹²

These central changes may be reflected in alterations in electrical activity.^{13,14} The electro-encephalographic signs of cannabis use in man are not clear cut. Early reports described a reduction in α -wave activity with an increase β -activity for up to 6 days after cannabis use,^{15,16} while others have demonstrated an increase in α -wave and a reduction in β -wave activity.^{17,18} Some studies demonstrated a dose-response relationship with altered electro-encephalographic patterns and suggested that a tissue tolerance to cannabis develops, since chronic users demonstrated these changes only with increasing doses of cannabis.^{17,19,20} Hollister *et al.*¹⁷ have suggested that these changes are nonspecific effects caused by relaxation and setting.

To date there is no convincing evidence that cannabis use causes brain damage, despite earlier reports of cerebral atrophy in cannabis users.^{17,21}

5 Lorraine Court, Cor Grant and William Avenues,
Norwood, Johannesburg

K. SOLOMONS, M.B. CH.B., D.O.H., D.T.M. & H., M.MED. (PSYCH.)
V. M. NEPPE, M.B. CH.B., B.A., F.F. PSYCH. (S.A.), M.MED. (PSYCH.), PH.D.,
F.R.C.P. (C.) (Present address: Division of Neuropsychiatry, Department of Psychiatry and Behavioral Sciences, RP-10, University of Washington, Seattle, Washington, USA)

Cannabis may exert anti-epileptic, anti-emetic and analgesic effects that have therapeutic implications. Cannabidiol has been associated with anti-epileptic properties; the anti-emetic and analgesic effects are associated with $\Delta 9$ -THC,^{14,22-24} which may also reduce intra-ocular pressure and has been used to treat wide-angle glaucoma.^{21,25} Its effects on reproductive function are uncertain. Reduced testosterone levels, oligospermia, impotence and gynaecomastia have all been reported.^{14,26} No sound evidence from human studies exists which shows teratogenic effects.²⁷ Respiratory function can be affected by bronchodilation, but bronchitis, sinusitis and obstructive airways disease may follow chronic irritation and deposition of tar so that its use in asthma has not been recommended.²⁸

Adverse psychological effects

Anxiety reactions may occur with acute cannabis intoxication as a 'bad trip' experience. Reactions may vary from mild restlessness to more severe states with depersonalisation, derealisation, a sense of loss of control, fear of dying, panic reactions and paranoid ideas. These adverse reactions may last for a few hours to a few days.²⁹ Flashbacks from cannabis abuse have been reported but these are infrequent when compared with other hallucinogens. The flashbacks are usually associated with 'good trips'.³⁰

A mild withdrawal state from long-term use has been described. It consists of irritability, restlessness, anorexia, insomnia, nausea, vomiting, diarrhoea and sweating. This reaction is based on the tolerance and mild physical dependence that develops. It is not thought to be severe enough to lead to drug-seeking behaviour.³¹ Other studies have failed to demonstrate tolerance and withdrawal phenomena.³²

Psychotic reactions

A wide variety of psychotic phenomena have been attributed to cannabis use. These include delusional thinking, paranoid ideas, paranoid psychotic reactions, visual and auditory hallucinations, acute brain syndrome, toxic psychosis, transient psychosis, acute and chronic mania, schizo-affective breakdown, schizophrenic reaction and schizophrenic psychosis.³³

A toxic psychosis caused by cannabis has been described.³⁴⁻³⁶ The syndrome consists of disturbed and sometimes aggressive behaviour, schizophrenic-like features of blunted affect and withdrawal, bewilderment, paranoid ideation and hallucinations, often all experienced in clear consciousness, and disappearance of the symptoms within a few weeks after discontinuation of cannabis use.³⁴⁻³⁶

A cannabis-associated manic psychosis has been described in a study of a rapidly resolving psychotic syndrome with minimal schizophrenic-type features.³⁷ The cannabis urinary metabolites were measured daily and the decline in metabolites closely paralleled the resolution of the psychotic mental state. The picture observed in this study was very similar to that described in an earlier study of cannabis-related mania.³⁸

There is an extensive overlap in symptoms and symptom-clusters in the extensive published reports on cannabis-related psychosis, but there is no widely accepted classification system or standardised diagnostic criteria for the diagnosis of toxic cannabis psychosis.³³⁻³⁵ This may be because unresolved controversies, such as whether organic features of consciousness, orientation, memory and other cognitive faculties need to be part of the presentation,^{34,37,39} and whether cannabis causes the psychosis in its own right or whether it precipitates an underlying predisposition to psychosis,³⁷ have not been clarified. An additional issue may be that the majority of reports of toxic

cannabis psychosis originate from Eastern, African and Third-World countries, not in developed Western countries where the enduring psychiatric classification systems originate.

The reasons for this uneven occurrence of cannabis psychosis have not been fully explained; they may relate to factors such as culture, genetic predisposition and differing potencies of the cannabis in different areas and countries.⁴⁰ There is at present no reliable way to predict who may be predisposed to cannabis psychosis when using high-potency cannabis.

Amotivation syndrome

An amotivation syndrome has been postulated as a long-term consequence of chronic cannabis use.⁴¹ It is thought to consist of diminished drive, volition and ambition, a loss of motivation, apathy, inactivity, self-neglect and a lack of concern about the future.^{42,43}

A Canadian Commission of Inquiry⁴² reviewed the evidence for the amotivation syndrome in the late 1960s. It found that most of the studies were from foreign, particularly oriental, countries and that most of the studies were methodologically flawed with results that were not generalisable. Most studies failed to take premorbid personality and sociocultural factors into account. Subsequent studies challenged the earlier reports on an amotivation syndrome and argued that a cannabis-induced amotivation syndrome probably does not exist.^{44,45} Some authors have ascribed the observed features of the amotivation syndrome to personality factors that predated cannabis use, as well as other socio-economic and family background factors.^{46,47} Other studies have suggested that, to the contrary, chronic cannabis use leads to no differences in productive work output and may in fact be taken to promote motivation among people performing fatiguing and monotonous work.^{44,48}

Data on the amotivation syndrome drawn from university student populations also suggest that drop-out rates are not causally associated with cannabis use but rather with background factors, such as closeness to parents, sociopolitical alienation, multiple drug use, parental education level, value orientations and pre-cannabis educational ambitions.^{49,50}

Some studies have reported a productivity decline as well as neuropsychological and personality changes in chronic cannabis users when tested in controlled experimental settings;⁴² these findings have not been confirmed by other researchers.⁵¹

An increased incidence of personality disorders has been reported, particularly the antisocial spectrum, often with a greater incidence of criminal records among chronic cannabis users compared with matched samples of non-cannabis users. This finding has been proposed as an alternate explanation for the higher drop-out rates and lower levels of social achievement noted among chronic cannabis users.^{52,53}

It is likely that the features indicative of the putative amotivation syndrome are due to either pre-existing personality or sociocultural factors. There is also a much higher risk that chronic cannabis users may be using other illegal drugs and that the amotivational symptoms may be related to this.^{44,47,54}

Cannabis use and other drugs

A number of studies have demonstrated that chronic cannabis use is associated with an increased incidence of use of 'harder' drugs such as cocaine, amphetamines, opiates, narcotics and lysergic acid diethylamide (LSD). Very few people who habitually use hard drugs do not or have not used cannabis at the same time or in the past. An association between chronic cannabis use and alcoholism has also been found.^{41,55}

Conclusion

Research with *Cannabis sativa* has been difficult to interpret. Probably the major single problem in this regard has been that low potency cannabis has neither been demonstrated to induce organic brain disease nor prolonged psychotic reactions. This contrasts markedly with the clinical picture that is seen in areas such as the RSA where high potency cannabis appears to induce more serious reactions. The differences may be caused by varying composition of Δ^9 -THC and other metabolites. The full impact of widespread cannabis use in the RSA in terms of psychiatric morbidity, road and industrial accidents and other indices of violence, still has to be elucidated.

REFERENCES

- Johnson KM, Ho BT, Dewey WL. Effects of delta-9-tetrahydrocannabinol on neurotransmitter accumulation and release mechanisms in rat forebrain synaptosomes. *Life Sci* 1976; **19**: 347-356.
- Johnson KM, Dewey WL. The effect of delta-9-tetrahydrocannabinol on the conversion of (³H) tryptophan to 5-(³H) hydroxytryptamine in the mouse brain. *J Pharmacol Exp Ther* 1978; **207**: 140-150.
- Weil AT, Zinberg NE, Nelson JM. Clinical and psychological effects of marijuana in man. *Science* 1968; **162**: 1234-1242.
- Gill EW. The effects of cannabinoids and other CNS depressants on cell membrane models. *Ann NY Acad Sci* 1976; **281**: 151-161.
- Hollister LE. Interactions of Δ^9 -tetrahydrocannabinol with other drugs. *Ann NY Acad Sci* 1976; **281**: 212-218.
- Renaud PF, Schuster LR, Heinrich R, Freedman DX. Marijuana: standardised smoke administration in dose-effect curves on heart rate in humans. *Science* 1971; **174**: 589-591.
- Johnson S, Domino EF. Some cardiovascular effects of marijuana smoking in normal volunteers. *Clin Pharmacol Ther* 1971; **12**: 762-768.
- Hollister LE. Actions of various marijuana derivatives in man. *Pharmacol Rev* 1971; **23**: 349-357.
- Weil AT. Adverse reactions to marijuana: classification and suggested treatment. *N Engl J Med* 1970; **282**: 997-1000.
- Waskow IE, Olsson JE, Salzman C, Katz MM. Psychological effects of tetrahydrocannabinol. *Arch Gen Psychiatry* 1970; **22**: 97-107.
- Tart CT. Marijuana intoxication: common experiences. *Nature* 1970; **226**: 701-704.
- Traub SH. Perceptions of marijuana and its effects: a comparison of users and non-users. *Br J Addict* 1977; **72**: 67-74.
- Domino EF, Hardman HF, Seevers MH. Central nervous system actions of some synthetic tetrahydrocannabinol derivatives. *Pharmacol Rev* 1971; **23**: 317-336.
- Hardman HF, Domino EF, Woods LA, Seevers MH. Pharmacological actions of Δ^9 -tetrahydrocannabinol derivatives. *Pharmacologist* 1970; **12**: 258.
- Wikler A, Lloyd BJ. Effect of smoking marijuana cigarettes on cortical electrical activity. *Fed Proc* 1945; **4**: 141-142.
- Ames F. A clinical and metabolic study of acute intoxication with *Cannabis sativa* and its role in the model psychoses. *J Mental Sci* 1970; **104**: 972-999.
- Fink M. Effects of acute and chronic inhalation of hashish, marijuana and Δ^9 -tetrahydrocannabinol on brain electrical activity in man: evidence of tissue tolerance. *Ann NY Acad Sci* 1976; **282**: 387-398.
- Hollister L, Sherwood S, Cavasino A. Marijuana and the human electroencephalogram. *Pharmacol Res Commun* 1970; **2**: 305-308.
- Cohen S. The 94-day cannabis study. *Ann NY Acad Sci* 1976; **282**: 211-220.
- Mendelson HH, Babor TF, Kuehule JC et al. Behavioral and biologic aspects of marijuana use. *Ann NY Acad Sci* 1976; **282**: 186-210.
- Campbell AMG, Evans M, Thompson LG, Williams MJ. Cerebral atrophy in young cannabis smokers. *Lancet* 1971; **2**: 1219-1226.
- Cunha JM, Carlini EA, Pereira AE. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 1980; **21**: 175-185.
- Chang AE, Shilling DJ, Stillman RC et al. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high dose methotrexate. *Ann Intern Med* 1979; **91**: 819-824.
- Sallan SE, Zinberg NE, Frei E. Anti-emetic effects of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *N Engl J Med* 1975; **293**: 795-797.
- Hepler RS, Frank IR. Marijuana smoking and intraocular pressure (Correspondence). *JAMA* 1971; **217**: 1392.
- Kolotny RC, Masters WH, Kolodner RM, Toro G. Depression of plasma testosterone levels after chronic intensive marijuana use. *N Engl J Med* 1974; **290**: 872-874.
- Leuchtenberger C, Leuchtenberger R, Zbinden J, Schleh E. Cytological and cytochemical effects of whole smoke and of the gas vapor phase from marijuana cigarettes on growth and DNA metabolism of cultured mammalian cells. In: Nahas GG, ed. *Marijuana: Chemistry, Biochemistry and Cellular Effects*. New York: Springer-Verlag, 1976.
- Tennant FS, Preble M, Pendergrast TJ, Ventry P. Medical manifestations associated with hashish. *JAMA* 1971; **216**: 1965-1969.
- Patterson CD. Self-reported unpleasant effects from illicit use of fourteen substances. *Br J Addict* 1974; **69**: 249-256.
- Stanton MD, Bardoni A. Drug flashbacks: reported frequency in a military population. *Am J Psychiatry* 1972; **129**: 751-755.
- Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. *Ann NY Acad Sci* 1976; **282**: 221-239.
- Wikler A. Aspects of tolerance to and dependence on cannabis. *Ann NY Acad Sci* 1976; **282**: 126-147.
- Bensusan AD. Drug pollution — the problem of abuse. *S Afr Med J* 1971; **45**: 834-838.
- Chopra JS, Smith JW. Psychotic reactions following cannabis use in East Indians. *Arch Gen Psychiatry* 1974; **30**: 24-27.
- Thacore VR, Shukla SRP. Cannabis psychosis and paranoid schizophrenia. *Arch Gen Psychiatry* 1976; **33**: 383-386.
- Knight F. Role of cannabis in psychiatric disturbance. *Ann NY Acad Sci* 1976; **282**: 64-71.
- Rottanburg D, Robins AH, Ben-Arie O, Teggin A, Elk R. Cannabis-associated psychosis with hypomanic features. *Lancet* 1983; **2**: 1364-1366.
- Harding T, Knight F. Marijuana — modified mania. *Arch Gen Psychiatry* 1973; **29**: 635-637.
- Thacore VR. Bhargava psychosis. *Br J Psychiatry* 1973; **123**: 225-229.
- Chopra GS, Jandu BS. Psychoclinical effects of long-term marijuana use in 275 Indian chronic users: a comparative assessment of effects of Indian and USA users. *Ann NY Acad Sci* 1976; **282**: 95-108.
- McGlothlin WH, West LJ. The marijuana problem: an overview. *Am J Psychiatry* 1968; **125**: 125-134.
- Campbell I. The amotivational syndrome and cannabis use with the emphasis on the Canadian scene. *Ann NY Acad Sci* 1976; **282**: 33-36.
- Boulougouris JC, Liakos A, Stefanis C. Social traits of heavy hashish users and matched controls. *Ann NY Acad Sci* 1976; **282**: 17-23.
- Comitas L. Cannabis and work in Jamaica: a refutation of the amotivational syndrome. *Ann NY Acad Sci* 1976; **282**: 24-32.
- Beaubrun MH, Knight F. Psychiatric assessment of 30 chronic users of cannabis and 30 matched controls. *Am J Psychiatry* 1973; **130**: 309-311.
- Carter WE, Doughty PL. Social and cultural aspects of cannabis use in Costa Rica. *Ann NY Acad Sci* 1976; **282**: 2-16.
- Halikas JA, Weller RA, Moise CL, Hoffman RG. Use of marijuana and other drugs among adult marijuana users: a longitudinal study. *Compr Psychiatry* 1984; **25**: 63-70.
- Partridge WL. Cannabis and cultural group in a Colombian municipio. In Ruben V, ed. *Cannabis and Culture*. Paris: Mouton, 1975: 147-172.
- Mellinger JD, Somers RH, Davidson ST, Manheimer DI. The amotivational syndrome and the college student. *Ann NY Acad Sci* 1976; **282**: 37-55.
- Brill NQ, Christie RL. Marijuana use and psychosocial adaptation. *Arch Gen Psychiatry* 1974; **31**: 713-719.
- Greenberg I, Mendelson JH, Kuehule JC, Mello N, Babor TF. Psychiatric and behavioral observations of casual and heavy marijuana users in a controlled research setting. *Ann NY Acad Sci* 1976; **282**: 72-84.
- Stafanis C, Liakos A, Boulougouris J, Fink M, Freedman AM. Chronic hashish use and mental disorder. *Am J Psychiatry* 1976; **133**: 225-227.
- Weller RA, Halikas JA. Marijuana use and psychiatric illness: a follow-up study. *Am J Psychiatry* 1985; **142**: 848-850.
- Kandel DB. Marijuana users in young adulthood. *Arch Gen Psychiatry* 1984; **41**: 200-209.
- Black S, Owens KL, Wolff RP. Patterns of drug use: a study of 5482 subjects. *Am J Psychiatry* 1970; **127**: 420-423.