Cannabis and cannabis withdrawal

D. E. Smith and R. B. Seymour

David E. Smith, M.D. President and Medical Director, Haight Ashbury Free Clinics, San Francisco, California, USA.
Richard B. Seymour, MA, Information and Education Director, Office of the President, Haight Ashbury Free Clinics, San Francisco, California, USA.

(Requests for offprints to: RBS, 90 Harrison C, Sausalito, CA 94965, USA) Manuscript accepted May 1996.

Cannabis, or marijuana, has been the subject of much controversy. The authors discuss the neuropharmacology of tetrahydrocannabinol (THC). They relate the recent identification of a THC receptor site in the brain and its possible relevance to the existence of a marijuana withdrawal syndrome. Such a withdrawal syndrome is described. The authors conclude by presenting their views on legalization of marijuana. They are against legalization and present their case from a public health perspective.

INTRODUCTION

Cannabis, or marijuana, is the most controversial illicit drug in use today. Its defenders maintain that marijuana is harmless, or at least less harmful than other drugs, including alcohol and tobacco, while its more virulent attackers claim it causes numerous sequelae, including birth defects more horrendous than those that resulted from thalidomide use. Much rhetoric has been expounded by both sides of the controversy. Unfortunately, even though there is ample evidence that cannabis is a dangerous substance, the extreme claims from both ends of the spectrum have tended to cloud the clinical reality of marijuana use, pharmacology and neurochemistry.

The confusion of claims about marijuana are also inhibiting prevention efforts in the USA, resulting in increased use among teenagers. The 1994 National Household Survey on Drug Abuse, compiled by the National Institute on Drug Abuse (NIDA) reported that approximately 7.3% of US teenagers, about 1.3 million between the ages of 12 and 17, smoked marijuana in the last year. This figure is up 4% from the 1992 Survey. It was noted that until 1992, marijuana use had declined every year since 1979 (NIDA 1994). Lee Brown, President Clinton's national drug policy coordinator, reported that marijuana accounts for 81% of illicit drug use in the USA, and its rise among teenagers reflects a growing belief that marijuana is benign. According to Brown, only 42% of teenagers considered marijuana a dangerous drug (San Francisco Chronicle 1995). This change in attitude, combined with the reversal in teen marijuana use, suggests that marijuana use will remain a significant public health and policy issue for the foreseeable future.

The danger of marijuana use has been further exacerbated in recent years by its increase in potency since the 1960s and 1970s. In the past, the most common marijuana cigarette smoked in the USA contained approximately 10 mg delta-9-tetrahydrocannabinol (THC). More recently, with the advent of selective breeding, there has been an increase in the THC content and potency of marijuana cigarettes. In addition, the use of 'hash oil', a concentrated tincture of hashish, with the marijuana leaf significantly increases the amount of THC in the combination cigarette (Gold 1989, 1994). This change in marijuana potency has been a primary factor in transforming the low-dose, self-experimentation of marijuana use typical in the 1960s to the high-potency, high-reward/reinforcement marijuana use and dependence prevalent in the 1990s. Properties that increase reinforcement potential, such as rapid absorption, high intrinsic pharmacological activity of a drug, and rapid entry into specific regions in the brain, are present in the high-potency THC of the 1990s. Similarly, the factors that favour physical dependence, such as long half-life, low clearance, cumulative drug load, and high intrinsic pharmacological activity, are also present.

NEUROPHARMACOLOGY OF MARIJUANA

While marijuana can be eaten, the most common mode of marijuana self-administration is by smoking and inhalation. Marijuana smoke contains more than 150 compounds in addition to the major psychoactive component, delta-9-THC. Many of the cannabinoids and other complex organic compounds appear to have psychoactive properties and others have not been tested for long- or short-term safety in animals or human beings.

The pharmacology of marijuana is complex, starting with the volatilized THC, produced by the burning of the cigarette and followed by deep inhalation. Marijuana is rapidly absorbed from the lungs and THC and major metabolites can be traced throughout the body and brain. In the past, there has been some debate over whether marijuana's main constituent, delta-9-THC, acts directly on the central nervous system (CNS) or whether it must first be metabolized to 11-OH delta-9-THC. It now appears that delta-9-THC is directly psychoactive (Lemberger et al 1976).

When marijuana is smoked, it appears to produce its psychoactive effects through specific binding with endogenous 'THC receptors'. Radioligand binding studies with a water-soluble cannabinoid have revealed high-affinity sites in the brain that are specific for cannabinoids and that can be inhibited by myelin-basic protein in the rat (Nye et al 1988). Anandamide (the name given to the structure of arachidonylethanolamide, an arachidonic acid derivative in the porcine brain) has recently been shown to inhibit the specific binding or a radiolabeled cannabinoid probe to synaptosomal membranes in a manner typical of competitive

THC is highly lipid-soluble and a complex relationship exists between THC, which can be measured in the blood after self-administration, and rapid transfer into lipid and other areas of the body and brain. Direct correlations between self-reports of euphoria and blood levels have been hindered by this relationship and the metabolism of THC in the liver into 11-hydroxy-THC and 11-nor-COOH-THC (Wall et al 1983) and tens of other metabolites with psychoactive properties. THC and THC metabolites are primarily excreted in the faeces. The slow release of THC and active metabolites from lipid stores and other areas may

ligands. This effect produces a concentration-dependent inhibition of the electrically evoked twitch response of the mouse vas deferens, a characteristic effect of psychotropic cannabinoids. These properties suggest that anandamide, may function as a natural ligand for the cannabinoid receptor (DeVane et al 1992). In the first in vivo examination of anandamide, Fride and Mechoulam (1993) reported that it produced hypothermia and analgesia, effects that parallel those caused by psychotropic cannabinoids. The identification of a THC receptor and its ligand helps to explain marijuana's analgesic, anti-nausea, concentration and memory problem effects. Thomas et al (1992) reported that the cannabinoid binding of two ligands was densest in the basal ganglia and cerebellum (molecular layer), with intermediate binding in layers I and VI of the cortex, and the dentate gyrus and CA pyramidal cell regions of the hippocampus. The identification of a THC receptor and its ligand also suggests the possible development of new pharmacological treatments for marijuana abuse.

Further verification of a THC receptor has recently been announced by NIDA (Swan 1995). Experiments involving the application of a THC antagonist, SR 141716A, produced a dramatic withdrawal syndrome in rats. According to senior investigator Billy Martin, 'The fact that people do seek treatment for marijuana dependence is evidence of marijuana withdrawal in humans.' Noting that withdrawal in humans is usually long and drawn out, he added, 'But with rats, using SR 141716A as an effective antagonist, we compress and accentuate that withdrawal process' (Aceto et al 1995).

explain the so-called carry-over effects on driving and other reports of behavioural changes over time. THC is stored in body fat and its slow excretion may make the urine test positive for more than 30 days, particularly if the individual is a chronic abuser. If the person is subject to drug testing in industry, the urine test can be positive, thereby putting the person's job in jeopardy, since the cut-off levels in industry are relatively low, i.e. 50μg to 100 μg. Even relatively low levels of use can be detected. This issue is further complicated by the fact that a prescription drug, Marinol (synthetic THC), used for glaucoma and the nausea associated with

cancer chemotherapy, can make the urine screen positive for THC. In drug testing, the medical review officer (MRO) makes the distinction between medical use and illicit use (Seymour & Smith 1990, 1994, Clark 1990).

EFFECTS OF MARIJUANA

Intoxication is similar to that experienced with other drugs. Marijuana is taken for the euphoria or 'high'. Marijuana is self-administered by laboratory animals and appears to have effects on the putative reward neuroanatomy similar to those of other drugs of abuse (Gardner & Lowinson 1991). A recent study found that THC treatment (like DA agonists) caused a decline in plasma prolactin levels accompanied by a decreased DOPAC/DA ratio in the medial basal hypothalamus, indicating that acute exposure to THC can augment brain DA neurotransmission (Rodriguez de Fonseca et al 1992). In addition, delta-9-THC binds with the mu-receptor, and opioid receptor subtype stimulated by morphine. Chronic mu-decreased LC activity could cause LC hyperactivity during withdrawal (Gold & Miller 1992). Furthermore, the opiate antagonist naloxone has been shown to attenuate the enhanced dopamine (DA) levels associated with delta-9-THC administration (Chen et al 1989). Again, opioid receptor interactions appear to be important for marijuana to exert its effects.

While future studies of delta-9-THC and its receptors in the brain will change our understanding of marijuana reinforcement, reward and withdrawal, naloxone's alteration of delta-9-THC effects suggests that marijuana engages endogenous brain opioid circuitry, causing an association between these endogenous opioids and DA neurons that appears fundamental to marijuana's euphoric effects.

MARIJUANA WITHDRAWAL SYNDROME

Chronic marijuana users often fit the profile for addictive disease, characterized by compulsion, loss of control, and continued use in spite of adverse consequences. In recovery, these individuals may respond well to such supported recovery fellowships as Alcoholics Anonymous (AA) and Marijuana Anonymous (MA). Subtle withdrawal symptoms may persist for extended periods of time, however, and it is not uncommon to hear chronic marijuana smokers in long-term

The identification of a THC receptor and ligand, and the recognition of the effect show release of THC and its active metabolites may have carry-over effects, may be of help in identifying and understanding a marijuana withdrawal syndrome. As recently as the publication of the American Society of Addiction Medicine's Principles of Addiction Medicine in 1994, authors in that work were reporting that, aside from mild increases in heart rate, blood pressure and body temperature, no clinically significant physiological withdrawal syndrome associated with discontinuation of marijuana use had been identified (Wilkins & Gorelick 1994).

These same authors point out that 'psychological manifestations' of marijuana withdrawal may include anxiety, depression, irritability, insomnia, tremors and chills. They add that these symptoms usually only last a few days, but subtle symptoms can persist for weeks. It seems curious that such symptoms as tremors and chills should be seen as psychological manifestations with no physiological basis, and one would hope that an increasing understanding of receptor site science, as it applies to marijuana, will help clarify the nature of marijuana withdrawal.

Ciraulo and Shader (1991) state that marijuana withdrawal syndromes are likely to resemble those commonly associated with ethanol withdrawal. They add that individuals chronically using cannabis are at high risk for such serious physical illnesses as pulmonary disease and also for developing concomitant polydrug abuse problems.

Our own experience at the Haight Ashbury Free Clinics and clinical discussions with colleagues who are treating marijuana users suggest the presence of a prolonged withdrawal syndrome, characterized primarily by anxiety and insomnia. We have also seen the onset of depression during withdrawal, particularly in adolescents suffering from motivation impairment manifested in learning difficulty and family relation problems during their marijuana use (Smith & Seymour 1982).

recovery comment that it was several years into abstinence and sobriety before they were truly aware of the adverse effects marijuana had on their thinking and behaviour.

LEGALIZATION OF MARIJUANA

Having reviewed the neuropharmacological and other evidence pointing to the existence of a THC withdrawal syndrome, we will conclude by turning to the issue of marijuana legalization and presenting our views on that volatile subject as well as our reasons for arriving at the conclusion that marijuana should not be legalized.

The proponents of legal reform pertaining to marijuana maintain that its use among adults should not be curtailed any more than that of alcohol or tobacco. Our own opinion that no currently illicit drug, including marijuana, should be placed on the open market as a legal substance, is based on public health considerations, and is in no small way influenced by the fact that the currently legal drug 'tobacco' is responsible for over 400 000 deaths a year in the USA. In addition, we are greatly concerned that, if marijuana were to be legalized, it would be distributed by the tobacco industry and marketed aggressively to youth in a fashion similar to that in which cigarettes are currently marketed. According to NIDA, 'Scientists at the University of California, Los Angeles, found that daily use of one to three marijuana joints appears to produce approximately the same lung damage and potential cancer risk as smoking five times as many cigarettes' (NIDA 1993). Is it wise to give ourselves permission to use freely yet another drug that is a know pulmonary toxin and potential carcinogen?

While the effects of chronic marijuana use on the lungs and pulmonary system are the most obvious physical threat from cannabis, these may just be the tip of the iceberg. Numerous medical studies suggest that marijuana may act as a general immunosuppressant, while clinical observation confirms that young people who start using tobacco and alcohol at an early age are at greater risk of moving on to marijuana use and addiction to such drugs as heroin and cocaine (DuPont 1984).

While we feel that the escalation of criminal penalties is not the answer for discouraging the use of marijuana among young people, we strongly support the concepts of education regarding the dangers of marijuana and other psychoactive drugs, early intervention, diversion to treatment from the criminal justice system, and treatment on demand for marijuana dependence. Understanding the dangers, education, prevention, and treatment represent for us the true course of a realistic program of 'harm prevention' based on clinical and public health realities.

REFERENCES

Aceto M D, Scates S M, Lowe J A, Martin B R 1995. Cannabinoid-precipitated withdrawal by a selective antagonist: SR 141716A. European Journal of Pharmacology 282 (1-3): R1-R2.

Chen J, Paredes W, Li J, Smith D, Gardner E L 1989. In vivo brain microdialysis studies of delta-9-tetrahydrocannabinol on presynaptic dopamine efflux in nucleus accumbens of the Lewis rat. Social Neuroscience Abstracts 15: 1096.

Ciraulo D A, Shader R I 1991. Clinical manual of chemical dependence. American Psychiatric Press, Washington/London, p. 186.

Clark H W 1990. The medical review officer and workplace drug testing. Journal of Psychoactive Drugs 22 (4): 435-445.

DeVane W A, Hanu L, Bruer A et al 1992. Isolation of a brain constituent that binds to the cannabinoid receptor. Science 258: 1946-1949.

DuPont R L 1984. Gateway drugs. American Psychiatric Press, Washington/London.

Fride E, Mechoulam R 1993. Pharmacological activity of the cannabinoid receptor agonist anandamide, a brain constituent. European Journal of Pharmacology 23 (2): 313-314.

Gardner E L, Lowinson J H 1991. Marijuana's interaction with brain reward systems: update. Pharmacology, Biochemistry and Behavior 40: 571-580.

Gold MS 1989. Marijuana. Drugs of abuse: a comprehensive series for clinicians, vol. 1. Plenum Publishing, New York.

Gold M S 1994. Marijuana. In: Miller N S (ed) Principles of addiction medicine. American Society of

Addiction Medicine, Washington.

Gold M S, Miller N S 1992. Seeking drugs/alcohol and avoiding withdrawal: the neuroanatomy of drive states and withdrawal. Psychiatric Annals 22 (8): 430-435.

Lemberger L, McMahon R, Archer R 1976. The role of metabolic conversion on the mechanisms of action of cannabinoids. In: Braude M S, Szara S (eds). Pharmacology of marijuana, vol 1. Raven Press, New York, p. 125-133.

National Institute on Drug Abuse 1993. Marijuana update. NIDA Capsules revised, September. The Institute, Rockville, MD.

National Institute on Drug Abuse 1994. The 1994 National Household Survey. The Institute, Rockville, MD.

Nye J S, Voglmaier S, Martenson R E, Snyder S H 1988. Myelin basic protein is an endogenous inhibitor of the high-affinity cannabinoid binding site in brain. Journal of Neurochemistry 50 (4): 1170-1178.

Rodriguez de Fonseca F, Fernadez-Ruiz J J, Murphy L L, Cebeira M, Steger R W, Bartke A, Ramos J A 1992. Acute effects of delta-9-tetrahydrocannabinol on dopaminergic activity in several rat brain areas. Pharmacology, Biochemistry and Behavior 42 (2): 269-275.

San Francisco Chronicle 1995. Teenage marijuana use nearly double since 1992, U.S. says. September 13.

Seymour R B, Smith D E 1990. Identifying and responding to drug abuse in the workplace. Journal of Psychoactive Drugs 22 (4): 383-405.

Seymour R B, Smith D E 1994. Controlling substance abuse in the workplace. In: LaDou J (ed). Occupational health & safety, 2nd edn. National Safety Council, Itasca, IL, p. 287-306.

Smith D E, Seymour R B 1982. Clinical perspectives on the toxicity of marijuana: 1967-1981. In: Marijuana and youth: clinical observations on motivation and learning. National Institute on Drug Abuse, Rockville, MD, p. 61-72.

Swan N 1995. Marijuana antagonist reveals evidence of THC dependence in rats. NIDA Notes 10 (6): 1 & 6.

Thomas B F, Wei X, Martin B R 1992. Characterization and autoradiographic localization of the cannabinoid binding site in rat brain using [3H]-OH-delta-9-THC-DMH. Journal of Pharmacology and Experimental Research 263 (3): 1383-1390.

Wall M E, Sadler B M, Brine D et al 1983. Metabolism, disposition and kinetics of delta-9-tetrahyrocanna-binol in men and women. Clinical and Pharmacological Therapy 34: 353-363.

Wilkins J N, Gorelick D A 1994. Management of phencyclidine, hallucinogen and marijuana intoxication and withdrawal. In: Miller N S (ed). Principles of addiction medicine. American Society of Addiction Medicine, Washington.