CURRENT TOPIC

Cannabis

P Robson

The robust weed christened *Cannabis sativa* by Linnaeus was humankind's first non-food crop, and the medicinal and psychoactive properties of the resin exuded from the flowering tops of the female plants have been recognised for at least 8000 years.[1] Today in Britain it is easily the most prevalent illicit drug; more than a third of A level students and over 50% of Oxford University undergraduates say they have sampled it.[2] On the other hand, its classification within Schedule 1 of the Misuse of Drugs Regulations (1985) denies British doctors the right to prescribe it under any circumstances, and effectively rules out prospective research on human volunteers or patients which might clarify its properties, both beneficial and adverse.

Chemistry and pharmacology

Inhale deeply from a cannabis 'spliff' and your lungs will be on the receiving end of hundreds of chemicals, at least 60 of which are psychoactive. Early cannabinoids to be isolated were cannabinol in 1905 and cannabidiol 30 years later, but the seminal discovery was that of the main active ingredient, delta-9-tetrahydrocannabinol (THC) in 1964.[3] Many related compounds were then identified which are characterised as aryl substituted meroterpenes.[4] In 1988 a specific protein receptor for THC was identified in nerve cells[5] and in 1992 Mechoulam and colleagues identified an endogenous ligand for this receptor which they called 'anandamide'.[6] In 1993 a second receptor was discovered in spleen macrophages.[7] This 'CX5' receptor is not present within the central nervous system and its existence raises the possibility of developing compounds devoid of psychoactivity.

The natural role of the cannabinoid receptor and the anandamide system have yet to be delineated, but may be concerned with mood, memory and cognition, perception, movement, coordination, posture and skeletal muscle tone, sleep, thermoregulation, appetite, and immune response.[8]

Therapeutic potential

Cannabis has been used as a medicine in China, India, the Middle East, southern Africa, and South America for centuries.[1 9] Accounts by Pliny and Galen have been familiar to European doctors for more than 1600 years. In the nineteenth century it was respectable enough to be used by Queen Victoria's doctor to alleviate her labour pains.

Today the only cannabinoid available for prescription in the UK is nabilone (Cesamet), a synthetic THC analogue. This has a licence which restricts its use to the treatment of nausea and vomiting caused by cytotoxic chemotherapy which is unresponsive to conventional antiemetic drugs. There is ample evidence from controlled trials conducted in the 1970s and 1980s that THC is at least as effective an antiemetic as other drugs then available.[10] Sedative and psychotropic effects limited its usefulness for some patients. No comparisons with the newer $5HT_3$ antagonists have been conducted, so its role in modern antiemetic regimens remains uncertain.

Of potential interest to paediatricians is a pilot study in which the non-psychotropic delta-8-THC was extremely effective in preventing vomiting in a small group of children receiving anticancer treatment, with minimal adverse effects.[11]

Many anecdotal reports exist of the beneficial effects of cannabis in a number of clinical disorders, but few of these claims have been investigated through adequately controlled trials. Because of the legal restrictions human research on cannabinoids has generally been focused on small samples using imperfect methodology and is therefore difficult to interpret. For example, many patients with multiple sclerosis have claimed that cannabis reduces spasticity and painful muscle spasms, and surveys among groups of patients seem to bear this out.[12] There is limited support from a small number of controlled studies,[13] but a negative effect on posture and balance (in common with other antispasticity drugs) may occur.[14]

There is no doubt that THC lowers intraocular pressure,[15] but a role in glaucoma treatment has yet to be explored. There is preliminary evidence that it may be an effective analgesic,[16] albeit with a high incidence of sedation at higher doses. THC has been shown to have significant appetite stimulating effects in patients with cancer[17] and those with AIDS.[18] This, alongside its antiemetic, analgesic, anxiolytic,[19] hypnotic,[20] and antipyretic[21] properties suggests the potential of a unique role in the management of these disorders, and is one of the most compelling areas for future research.

Chilton Clinic, Warneford Hospital, Oxford OX3 7JX

Correspondence to:
Dr Robson.

Adverse effects of cannabis

This subject has been reviewed exhaustively by Hall *et al* in a widely admired report.[22] The acute effects include anxiety, panic, and paranoia; impairment of attention and memory; psychomotor impairment leading to the risk of accidents on the roads or elsewhere; psychotic symptoms in vulnerable patients; and the chance of low birthweight infants when used in pregnancy.

Hall *et al* concede that the effects of long term heavy use remain uncertain. They conclude that the probable risks are respiratory diseases associated with smoking (cannabis smoke contains more carcinogens and insoluble particulates than that of tobacco), the development of a cannabis dependency syndrome and subtle forms of cognitive impairment which may or may not be reversible after prolonged abstinence. Possible risks are an increased incidence of cancers of the mouth, airways, and oesophagus; an increased prevalence of leukaemia and birth defects among children of mothers who used the drug during pregnancy; and educational and occupational underachievement.

Hall *et al* identify groups which may be particularly vulnerable to adverse effects. These include adolescents already troubled by poor school performance or those experimenting with cannabis in their early teens, pregnant women, and subjects with pre-existing mental or physical disease. They draw attention to the uncertain implications of the growing availability of more potent cannabis products on the black market. They also stress that 'the probable and possible adverse health and psychological effects of cannabis need to be placed in comparative perspective [to those of alcohol and tobacco] to be fully appreciated'.

Long term consequences of cannabis use

Cross sectional surveys are not informative about the consequences of drug use because they cannot distinguish between cause and effect. For example, the finding that most heroin addicts began their illicit drug career by smoking cannabis does not, as some have claimed, prove that experimenting with cannabis leads on inexorably to harder drug use. Almost everyone who tries cannabis has previously smoked cigarettes and guzzled alcohol, but nobody would claim that one caused the other, or that tea and coffee originally set the whole sequence in motion. Most cannabis smokers never try another illegal drug.

There are a handful of prospective long term studies[23–28] which have followed up children through the adolescent years into adulthood and a number of conclusions can be drawn from these. Most illicit drug use is experimental, transient, or occasional, and this pattern does not seem to be associated with measurable long term harm. In one study it was found that cigarettes were more disruptive to health than alcohol, cannabis, or even 'hard' drugs.[24] On the other hand, an early onset of legal or illegal recreational drug use or significant escalation in the teenage years has a strong association with later mental and physical problems, difficult family, social, and sexual relations, and disruption of education and employment. Problem drug use, which is often associated with delinquency, teenage pregnancy, and school dropout, is much more likely to be a symptom than a cause of personal and social maladjustment.[26]

The legalisation debate

Cannabis is the focus for over 85% of all drug seizures and its users account for more than 80% of people charged with drug offences (40 000 in 1991). The first argument for decriminalisation is that this does not seem a sensible prioritisation: many people would feel that a greater preoccupation with heroin or crack cocaine might be appropriate. Price and availability are generally taken as the key markers for the success or otherwise of the 'war on drugs' and do not suggest that this is money well spent; in relative terms the first has come down and the second has gone up. The illegality of cannabis forms part of the windfall to organised crime that prohibition provides, criminalises a section of the population who would not otherwise dream of committing any offence, and necessitates contact with the underworld to obtain a supply. Alcohol and tobacco are arguably more toxic and addictive than cannabis, and the intoxication associated with alcohol is much more dangerous and disruptive. Internal restraint reinforced by family, peer, and cultural pressure (which restrains alcohol use effectively in most of the population despite unprecedented availability and promotion) is far more powerful than external restraint (that is, legal coercion). Growing cannabis in the greenhouse for personal consumption is a classic 'victimless crime'; it may prove damaging to the individual, but eggs and cream are not controlled just because overindulgence may cause heart attacks. Cannabis has been valued as a medicine for thousands of years—why veto it now in preference for more toxic and expensive alternatives? Scheduling a drug used by millions of people in such a way as to prevent human research into its risks and benefits does not seem rational.

Those who oppose decriminalisation argue that such a move would greatly increase the numbers who would try cannabis and consequently its casualties. This effect would be heightened by the inevitable involvement of commercial entrepreneurs who would actively promote their new product. There would be a financial impact on the NHS and social services. Making the drug available on prescription would give the wrong message on the streets and make recreational use more likely. Minors would still presumably be restricted from access, so a black market would continue to exist. Apart from all this, Britain would be out of step with most other countries and in breach of existing international agreements on drug control.

It is a matter of personal opinion which set of arguments carries most weight. Both sides of the debate are founded on speculation rather than fact, and fuelled by emotion and undeclared agendas rather than cool consideration

of existing problems and possible solutions. A fuller analysis of the issues was given by Robson in 1994.[29]

Conclusions

Despite the 'war on drugs', cannabis is cheap and easily accessible in most British schools. If the experience of alcohol is indicative, the increased availability of cannabis would be associated with wider usage. This may have more to do with active commercial promotion than simply ease of access. A survey among Oxford undergraduates (L Sell, P Robson, unpublished data 1994) suggested that few of those who had not yet experimented with cannabis would be tempted to do so if it were decriminalised. The Dutch introduced de facto decriminalisation of cannabis for personal use 25 years ago, but do not appear to have studied the sociological and medical impact of this in any formal way.

If cannabis use among young people did increase as a result of decriminalisation, would this replace other forms of intoxication, or add to them? Would the commercial interests of legal manufacturers drive the development of alternative delivery systems such as aerosols which would obviate the need to smoke the drug? Would the removal of illicit status reduce its appeal to some people and lead to an increase in consumption of some other substance? Would more potent forms come to dominate the market, resulting in a higher incidence of acute adverse effects in occasional users? There are many other uncertainties and although the arguments for decriminalisation are compelling, any move in this direction must be treated as a piece of social research and carefully monitored.

Given the existing prevalence of cannabis use, the complete absence of coordinated and controlled human research into the possible beneficial and adverse effects seems indefensible. Many doctors believe that cannabis and its derivatives should be available once again on prescription.[30] Decriminalisation appears politically unacceptable to all three UK parties for the time being but, in my opinion, the UK Government should open the door to both scientific investigation and medical use by rescheduling cannabis and its derivatives under the Misuse of Drugs Regulations at the earliest opportunity.

1 Mechoulam R. The pharmacohistory of cannabis sativa. In: Mechoulam R, ed. *Cannabinoids as therapeutic agents.* Boca Raton: CRC Press, 1986.
2 Robson P. Young people and illegal drugs. In: Macfarlane A, ed. *Adolescent medicine.* London: Royal College of Physicians of London, 1996.
3 Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. *J Am Chem Soc* 1971;**86**:1646-7.
4 Evans FJ. Cannabinoids: the separation of central from peripheral effects on a structural basis. *Planta Medica* 1991;**57**:S60-7.
5 Devane WA, Dysarz FA, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol* 1988;**34**:605-13.
6 Musty RE, Regio P, Consroe P. A review of recent advances in cannabinoid research and the 1994 international symposium on cannabis and the cannabinoids. *Life Sci* 1995;**56**: 1933-40.
7 Munro S, Thomas KL, Abu-Shaar M. Molecular characterisation of a peripheral receptor for cannabinoids. *Nature* 1993;**365**:61-5.
8 Pertwee RG. Pharmacological, physiological and clinical implications of the discovery of cannabinoid receptors: an overview. In: Pertwee R, ed. *Cannabinoid receptors.* London: Harcourt Brace, 1995.
9 Grinspoon L, Bakalar JB. *Marihuana, the forbidden medicine.* New Haven: Yale University Press, 1993.
10 Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG. Recent clinical experience with dronabinol. *Pharmacol Biochem Behaviour* 1991;**40**:695-700.
11 Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sci* 1995;**56**:2097-102.
12 Consroe P, Musty R, Tillery W, Pertwee RG. The perceived effects of cannabis smoking in patients with multiple sclerosis. *Proceedings of the International Cannabinoid Research Society*, 1996:7.
13 Ungerleider T, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. *Adv Alcohol Subst Abuse* 1987;7:39-50.
14 Greenberg HS, Werness SAS, Pugh JE, Andrus RO, Anderson DJ, Domino EF. Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. *Clin Pharmacol Therapeutics* 1994; **55**:324-8.
15 Hepler RS, Frank IM, Petrus R. Ocular effects of marihuana smoking. In: Braude MC, Szara S, eds. *The pharmacology of marihuana.* New York: Raven Press, 1976.
16 Noyes R, Brunk SF, Avery DH, Canter A. The analgesic properties of delta-9-THC and codeine. *Clin Pharmacol Ther* 1975;**18**:84-9.
17 Regelson W, Butler JR, Schulz J, *et al.* Delta-9-THC as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. In: Braude MC, Szara S, eds. *The pharmacology of marihuana.* Braude MC, Szara S, eds. New York: Raven Press, 1976.
18 Beal JE, Olson R, Laubenstein L, *et al.* Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 1995;**10**:89-97.
19 Fabre LF, McLendon D. The efficacy and safety of nabione (a synthetic cannabinoid) in the treatment of anxiety. *J Clin Pharmacol* 1981;**21**;377S-82S.
20 Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol* 1981;**21**:417-27.
21 Formukong EA, Evans AT, Evans FJ. The medicinal use of cannabis and its constituents. *Phytotherapy Research* 1989; **3**:219-31.
22 Hall W, Solowij N, Lemon J, eds. *The health and psychological consequences of cannabis use*. Canberra: Australian Government Publishing Service; 1994. National Drug Strategy Monograph Series No 25.
23 Kandel DB, Davies M, Karus D, Yamaguchi K. The consequences in young adulthood of adolescent drug involvement. *Arch Gen Psychiatry* 1986;**43**:746-55.
24 Newcomb MD, Bentler PM. The impact of late adolescent substance use on young adult health status and utilization of health services: a structural equation model over four years. *Soc Sci Med* 1987;**24**:71-82.
25 Newcomb MD, Bentler PM. Impact of adolescent drug use and social support on problems of young adults: a longitudinal study. *J Abnorm Psychol* 1988;**97**:64-75.
26 Shedler J, Block J. Adolescent drug use and psychological health: a longitudinal enquiry. *Am Psychol* 1990;**45**:612-30.
27 Hawkins JD, Catalano RF, Miller JY. Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance abuse prevention. *Psychol Bull* 1992;**112**:64-105.
28 Newcomb MD, Scheier LM, Bentler PM. Effect of adolescent drug use on adult mental health: a prospective study of a community sample. *Experimental and Clinical Psychopharmacology* 1993;**1**:215-41.
29 Robson P. Drug policy—a need for change? *Forbidden drugs.* Oxford: Oxford University Press, 1994.
30 Meek C. Doctors want cannabis prescriptions allowed. *BMA News Rev* 1994;Feb:15.