CANNABIS

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Introduction

This review was compiled subsequent to recent reports from the House of Lords[1] and the Police Federation[2]. It aims to summarise the important additions to the published literature over the past two years, and to provide an easy source of references. Articles were identified by Medline search, by a systematic review of the major journals, and by consultation with other experts in the field. It is intended to be comprehensive.

1) Cannabis: The Scientific and Medical Evidence. House of Lords Select Committee on Science and Technology. **The Stationery Office, London** 1998.

2) Drugs and the Law: Report of the Independent Inquiry into the Misuse of Drugs Act 1971. The Police Foundation. **www.druglibrary.org/schaffer/Library/studies/runciman**. 1999.

A UK Prevalence/Availability/Price

Population Surveys

The latest figures from the British Crime Survey[A1] show that Cannabis remains the most commonly used drug in the UK, and that patterns of use have been stable over the last few years. Cannabis has been used by 27% of the adult population during their lifetime, by 9% within the last year and by 6% in the last month. The number of 16-19 year olds using Cannabis in the last year had fallen from 28 % in 1998 to 25%, whilst the same measure in 20-24 year olds had risen from 26% to 27%.
UK Drug Situation 2000, the UK Report to the European Monitoring Centre for Drugs and Drug Addiction[A2] contains original data collected in 1999 and a collation of other recent epidemiological research. Lifetime rates of Cannabis use for schoolchildren (11-16) were 11.8% in England and 16.0% in Scotland. The age of initiation was seldom before 13 (1.7% in England, 3% in Scotland). The Home Office reported from 1998 that of 153,200 people dealt with for drug offences, 76% involved Cannabis. Customs estimate that up to 80% of Cannabis resin entering the UK comes by sea from Morocco, with South Asia (Pakistan) accounting for the rest. Herbal Cannabis usually comes from Jamaica. 94.4% of seizures of Cannabis were made by the Police. The price of Cannabis remained stable between 1995 and 1999 (£3.28-£4.02 per gram).
The Department of Health has commissioned a study into long term heavy Cannabis use.

Prevalance in Specific Populations

A survey carried out on behalf of the Department of Health[A3] of schoolchildren in England (aged 11-16) again showed Cannabis to be by far the most widely used drug, with a reported usage rate of 12% across the group, and 28% of 15-16 year olds. Miller and Plant[A4], in a UK school survey of 15-16 year olds, found that 7.6% of pupils were heavy users (40 or more occasions). Respondents were asked about their lifetime drug use in a school survey[A5] (N=2558) of 14-16 year-olds in neighbouring urban (Dundee) and rural (Perth and Kinross) areas. Rates of Cannabis use were 43.0% (Dundee) and 42.4% (Perth and Kinross). There were no significant differences between regions, and drug use was unrelated to socio-economic measures, suggesting that "adolescent drug use in Scotland is not particularly concentrated in areas of urban deprivation". Wright[A6] surveyed the knowledge and experience of illicit drugs among 14-15 year olds in Wolverhampton in 1999 (N=274). The survey had been carried out every 5 years since 1969, and the findings suggested that the dramatic increase in those offered drugs, or knowing of someone taking drugs, had levelled off since 1994.

A cohort of medical students was surveyed for alcohol and drug use as second year and then fifth year students, and again after completing pre-registration house jobs[A7]. On the third occasion 66% reported lifetime use of Cannabis, and 24% were current users (compared to 22% when surveyed as final year students). All those who used Cannabis were heavy drinkers, and all those who used other illicit drugs had also used Cannabis. Cannabis use at entry to medical school was significantly related to alcohol use and personality measures of psychoticism[A8]. 2nd-year medical students in Leeds (N=136) self-reported drug use (time period not stated) of any drug: 28.3% men, 35.6% women; of which Cannabis was by far the most common (84.6% of men, 93.8% of women)[A9]. 55% of dental students reported some use of Cannabis during their training, with 8% using at least once a week[A10].

Mental health keyworkers completed a drug questionnaire on service users with severe mental illness[A11], and recorded problematic use of Cannabis in 10.2%, associated with males with psychotic disorders. A survey of patients with schizophrenia in central London found lifetime use of Cannabis in 18.9%, but the rate was 52.2% in those under 36 years of age[A12].

Winstock[A13] surveyed readers of a dance music magazine, and found very high rates of Cannabis use (73% in past month) and high rates of poly-drug use.

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B Prevalence in Other Countries

USA and Canada

A Canadian national survey from 1994[B1] gave figures of 29.3% for lifetime Cannabis use, 7.3% within the past year and 2.0% within the past week. Johnson[B2] discussed changes in reported rates of use from National Household Surveys on Drug Abuse between 1961 and 1990, and identified conflicting vectors of social forces: since the 1970s, social policies have acted to reduce drug use, while changes in childhood socialisation have led to increased use. The latter has been more marked in females, and has led to a convergence in use between genders.

A study by the USA Department of Health of 11-16 year old school students has measured drug use in successive cohorts from 1991-2000[B3]. The latest figures show Cannabis is by far the most commonly used drug. Among 15-16 year olds 37% reported use in the past year, and 6.0% were heavy users. There has been a gradual decline in use among 11-12 year olds since 1996, but rates for older students have not changed significantly. A postal questionnaire survey of USA college students[B4] (aged 18-24) in 1993, 1997 and 1999 (N= approx 15000 each time) found that prevalence of Cannabis use in the past month increased from 12.9% in 1993 to 15.7% in 1999. 91% of users also smoke, binge drank and/or used other illicit drugs. Although the increase may reflect earlier increases in secondary schools, about 33% initiated their drug use at college. Aitken[B5] reported data from the National Longitudinal Survey of Labor Market Experience of Youth (NLSY), N=8885, in 1984 and 1994. The figures reported for lifetime use were 64.7% in 1984 and 65.7% in 1994. There was good consistency of reporting over the 10-year period (>90%)[B6]. Another study found significant rates of "recanting" (up to 25%) when a repeat questionnaire was administered to USA college students[B7], which questions the validity of retrospective self-report data. This was more likely to happen in light users. Prevalence rates for current Cannabis use among homosexual men in six USA cities ranged from 34% to 50%[B8].

High rates of Cannabis use are found among individuals with a diagnosis of substance use disorder. Hser[B9] interviewed 242 male heroin addicts 33 years after they entered a treatment programme. 20.7% tested positive for opiates, and 35.5% admitted using Cannabis during the previous year. In 201 adults admitted to a chemical dependency testing centre, those meeting the criteria for conduct disorder were more likely to use Cannabis than those who did not[B10], and this finding was replicated among adolescents with substance use disorder[B11]. 24% of patients seeking treatment for alcohol dependence (N=248) were current Cannabis users[B12] A study of patients admitted to a psychiatric hospital found that Cannabis use disorder was less common than alcohol, but more common than any other drug[B13]. Factors predicting Cannabis use disorder were never being married, and having fewer admissions in the preceding 6 months. Only 24 of 333 suicide cases (7%) in Alabama between 1990 and 1998 tested positive for Cannabis at post-mortem, while alcohol was detected in 30%[B14].

Among offenders, Cannabis dependence was seen in 23 of a series of 50 adolescents (46%) admitted to a juvenile detention centre, and the rate was higher in detainees who also had a mood disorder[B15]. Boyd and Faith[B16] describe how the process of criminalisation and incarceration of female drug users in Canada may lead to a higher incidence of drug problems among female offenders.

Warner[B17] found a higher prevalence of alcohol and drug use disorders among adolescents in the USA compared with Puerto Rico, but few other differences in the profile of problem drug users. Black ethnicity predicted progression from licit to illicit drug use in a survey of 8550 USA high school students[B18]. In a high school survey of American Indian adolescents[B19], 40% reported using Cannabis in the last month. Males were more likely to be heavy users but not light users. There was a strong association with use of alcohol and other substances.

ElSohly[B20] presents data from the analysis of confiscated samples in the USA. In nearly every year, since 1980, more than 80% of samples were Cannabis. The potency (delta-9-THC content) slowly increased from 1.5% in 1980 to 4.5% in 1997.

Australia and New Zealand

Prevalence data is reported from the National Survey of Mental Health and Well-Being. This was a household survey of Australian adults, and ICD10 diagnoses were obtained using the CIDI (N=10641). The 12-month prevalence of ICD10 alcohol use disorder was 6.5%; of another drug use disorder 2.2%; harmful use of Cannabis 0.1%; Cannabis dependence 1.6%. The M:F ratio for each disorder was between 2:1 and 3:1. Associated factors were unemployment, never being married and being born in Australia[B21]. Cannabis use was associated with increased rates of mental health disorders[B22].

A population-based cohort study of Australian adolescents (N=2032), initially aged 14-15, was conducted over a 3-year period[B23]. Cannabis use was assessed by self-report.

	Mid-school (approx. age 14)	Late school (approx. age 16)
Prevalence of any Cannabis use	21%	28%
Using weekly or more	6%	10%

Mid-school use was more common in males and was associated with peer group use (strongest association), antisocial behaviour, daily smoking, high dose alcohol use and divorced or separated parents. Late-school onset of use was associated with the same factors, except for gender. Progression to heavy use was predicted by male gender, being born in Australia, high peer group use (in males) and early drinking and antisocial behaviour (in females). 12% of early users escalated to heavy use later on. When the same cohort was surveyed as young adults (average age 21), 17% were regular users and 7% met criteria for Cannabis dependence[B24]. Further data have been published from the 1998 National Drug Household Survey of Australian adolescents (age 15-19, N=1581)[B25]. Lifetime use was 45.2 %, with 9.4% currently heavy users. A substantial increase was seen in the use among young females since the previous survey in 1995. A significantly lower use of Cannabis was found among adolescents in Sydney who were Vietnamese- or Arabic- speaking, compared with English speakers[B26]. Urine samples were positive for Cannabis in around 60% of males detained by the police who agreed to provide a sample[B27].

Fergusson and Horwood[B28] describe the use of Cannabis in a New Zealand birth cohort at age 21 (Christchurch Health and Development Study, N=1265). Lifetime use was 69%, with DSMIV Cannabis dependence in 9% of the cohort. Risks for dependence were male gender, Maori ethnicity, cigarette smoking, conduct problems, delinquent peers and novelty seeking. A longitudinal study of the Dunedin Multidisciplinary Health and Development Study birth cohort reported rates of Cannabis use (over 50%) and dependence (10%) that were stable between age 21 and 26. Cannabis dependence, as distinct from occasional use, was associated with higher rates of hard drug use[B29].

Hall and Swift[B30] found only a modest increase in THC content of Cannabis is recent years, and suggested that the increase in Cannabis-related problems among young Australians was more likely to be due to earlier and heavier use. Poulsen[B31] found no increase in THC content of Cannabis plants seized in New Zealand between 1976 and 1996, and a decrease in the THC content of Cannabis oil since 1985.

Europe

Using data from the Early Developmental Stages of Psychopathology study in Munich, Germany, Perkonigg[B32] found rates of Cannabis use similar to those in USA studies. 30-35% of 14-17 year-olds (N=1228) had ever used Cannabis, although the lifetime incidence of DSMIV Cannabis abuse or dependence was low at 3.5%. Levels of use were fairly stable at

follow-up interview (average 19 months), and there was a low spontaneous remission rate (30-40%) among those with a DSMIV diagnosis.

A study of French adolescents (N=256, age 16-19)[B33] reported rates of lifetime use (49%) and DSMIV dependence (19%) that were higher than those in Germany. Urine samples were positive for Cannabis in 31 of 49 patients attending a Methadone centre (63%)[B34]. Lower rates were found in a 1998 self-report survey of Greek adolescents (age 13-18, N=8557)[B35]. The reported lifetime use of Cannabis was 12.6%, lower than that for inhalants, although the perceived availability of Cannabis had increased, and its perceived harm had decreased, since previous studies in 1993 and 1984. 34% of young men in Piedmont (Italy) had ever used Cannabis, but almost 80% of these had never used any other drug[B36]. 41% of students at universities in Gdansk, Poland, reported lifetime use of Cannabis[B37].

The Rest of the World

The Third National Study for the Consumption of Drugs was carried out in 1998 by the National Board for Narcotics Control in Chile (N=31665, age 18-64)[B38]. It reported lower lifetime use of Cannabis (16.8%) and use in preceding month (2.2%) than in the USA. Rates were also reported to be lower in high school students in Bogota, Colombia[B39] and adolescents in South-West China (lifetime use of Cannabis 0.3%, N=2649)[B40].

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C Harmful Effects of Cannabis

Reviews

The harmful effects of Cannabis have been reviewed by Hall[C1], by Farrell and Ritson[C2], and by Ashton[C3]. Hall concentrates on the public health burden of Cannabis use, predominantly among young people. He concludes that although the current literature does not suggest the toxic effects equate to those of tobacco, there is such a paucity of public health research that it is difficult to frame rational public health policies. Farrell and Ritson separate the medicinal and recreational uses, and conclude that the body of knowledge and the social response to Cannabis are still evolving. Ashton reviews the psychological (mood, perception, cognitive, psychomotor/driving, dependence) and systemic (CVS, respiratory, immunosuppressant and teratogenic) effects, concluding that "Cannabis is not … a harmless drug", and noting that some adverse effects may have a long latent period.

Cannabis Dependence

Farrell[C4] asserts a clear dependence pattern in a small percentage of those who use Cannabis. The symptoms of withdrawal are relatively mild, and the meaning of the diagnosis for sufferers is not yet clear. Several studies have sought to clarify the symptoms of Cannabis withdrawal. 54 outpatients seeking treatment for Cannabis dependence completed a 22-item Marijuana Withdrawal Symptom checklist, and the majority had 6 or more symptoms rated moderate or severe, providing support for a "cluster of withdrawal symptoms"[C5]. In a subsequent study 12 daily users were assessed daily for 16 days, including 2 periods of 3 days' abstinence, using the same withdrawal symptom checklist[C6]. Reliable withdrawal symptoms included craving for Cannabis, decreased appetite, sleep difficulty and weight loss, and the syndrome was similar to nicotine withdrawal in type and magnitude. When chronic users underwent a supervised 28-day abstinence period symptoms included anxiety, irritability, physical tension, decreased mood and appetite. Symptoms were most pronounced in the first 10 days but could last for the whole 28-day period[C7].

Several community population studies have attempted to measure the prevalence of Cannabis dependence. An Australian adult community sample[C8] (National Survey of Mental Health and Wellbeing, N=10641, age 18+, CIDI used for ICD10 and DSMIV diagnosis) showed that 7.1% had used Cannabis more than 5 times in the past year (Cannabis Users). The prevalence of DSMIV abuse and dependence were reported as follows:

In population: 2.2% met DSM criteria (1.5% dependence, 0.7% abuse)
1.7% met ICD criteria (1.6% dependence, 0.1% other)
Among Users: 31.7% met DSM criteria (21% dependence, 10.7% abuse)
23.6% met ICD criteria (22% dependence, 1.6% other)

The most common features were withdrawal symptoms and attempts to control use. The least common was neglecting other activities. Cannabis dependence was related to abuse and dependence of other substances[C9]. A German metropolitan random sample[C10] (Early Developmental Stages of Psychopathology, N=2446, age 14-24, born 1970-81, CIDI used for DSMIV diagnosis, re-interviewed after mean 42 months) found that males had an earlier age of onset of use and dependence than females. The later birth cohort (1977-81) had an earlier age of onset of use and dependence than the earlier cohort (1977-81), and was more likely to have increased use or become dependent at follow-up. Prevalence was as follows:

Cumulative lifetime incidence: 47% for use, 5.5% abuse, 2.2% dependence

A study of adults aged 19-21 (N=1803) from South Florida and containing a high proportion of Hispanics found annual rates of 6.5% for Cannabis abuse (lifetime 11.8%) and 7.0% for dependence (lifetime 11.7%)[C11].

The Baltimore Epidemiologic Catchment Area research group followed a cohort of 599 Cannabis users from the community for 15 years and found that 6.2% showed the dependence syndrome[C12]. Withdrawal symptoms were not found to be a prominent feature. An Australian

database sample of Cannabis users (N=200) were followed-up at 12 months (N=162)[C13]. 92% had lifetime DSMIIIR dependence at baseline, 77% in previous year. At follow-up, 70% had dependence in the previous year. Kandel and Chen performed a cluster analysis on a community sample of Cannabis users (N=708) which suggested 4 types: early onset-heavy use, early onset-light use, mid onset-heavy use, late onset-light use[C14]. The majority of those with early onset did not become heavy users.

Heishman, Singleton and Liguori present and validate a Marijuana Craving Questionnaire[C15]. Four specific constructs are compulsivity, emotionality, expectancy and purposefulness.

Medical Complications

A) Respiratory effects

Hall[C16] emphasises the significant risks to heavy smokers of Cannabis, particularly in those who also smoke tobacco. Significant respiratory symptoms and decreased respiratory function were found in young Cannabis smokers, independent of tobacco use, and equating to smokers of 1-10 cigarettes per day[C17]. Cannabis has been reported to be contaminated with Aspergillus spores, presenting a rsik of respiratory disease to the immunocompromised[C18].

B) Carcinogenesis

Dorrell[C19] reviews the possible carcinogenic effects mediated by the immunosuppression of delta-9-THC. A case of transitional cell carcinoma of the renal pelvis is reported in a heavy Cannabis smoker[C20].

C) CVS disease

Recent Cannabis ingestion has been implicated in sudden cardiovascular death in a case series of 6 young adults[C21], as tetrahydrocannabinol was found in postmortem blood samples in the absence of any other toxic substances. Another fatality occurred in a young man with rheumatic heart disease after ingestion of Bhang (a Cannabis preparation)[C22]. Herning[C23] used Doppler sonography to demonstrate increased cerebrovascular resistance (comparable to normal 60 year-olds) in young Cannabis abusers. Two cases of atrial fibrillation are reported following Cannabis smoking, suggesting that delta-9-THC may have effects on adrenergic systems[C24]. Mittleman[C25] used a case-crossover study design to calculate a relative risk for MI of 4.8 in the hour after smoking Cannabis. A cerebellar infarct is reported in a 15 year-old male related to heavy Cannabis use[C26].

D) Allergic reaction

Perez[C27] describes a severe allergic reaction to injected crushed Cannabis leaves.

Psychological/Psychiatric Complications

A) Reviews

Johns[C28] gives an overview of the psychological responses to Cannabis, effects on pre-existing mental illness, Cannabis as a risk factor for mental illness, dependency and withdrawal effects.
Glass[C29] describes the importance of Cannabis and endogenous cannabinoids in neurodegenerative disorders including schizophrenia.

B) Mental disorders

Data from a longitudinal study[C30] (Dunedin Multidisciplinary Health and Development Study, N=1139) were analysed to measure Cannabis use and the presence of mental disorders (using DIS for DSMIIIR) at ages 15, 18 and 21. Mental disorders (conduct disorder, alcohol or drug dependence and to a lesser extent anxiety/depression) were related to Cannabis use. At younger ages mental disorder predicted Cannabis use. At older ages,

Cannabis use predicted mental disorder (mostly substance dependence and antisocial behaviour).

Schizophrenia

An investigation of the relationship between Cannabis use and the onset of Schizophrenia described twice the rate of Cannabis use as in matched normal controls[C31]. Male sex and early symptom onset were risk factors for Cannabis use. A literature review[C32] confirmed an association between the use of various substances and violence in patients with Schizophrenia. An association has been reported between a cannabinoid receptor type 1 polymorphism and a subtype of schizophrenia[C33].

Bipolar Disorder

Strakowski[C34] suggested an association between Cannabis use and the duration of manic episodes in 50 patients.

Substance Disorder

Shillington[C35] found that users of both alcohol and Cannabis were more likely than drinkers alone to develop substance use problems. Problem drinkers who also used Cannabis had more negative consequences of their alcohol use and a worse outcome at 6 months[C36].

Depression and Anxiety

Analysis of 15-year follow-up data from the Baltimore Epidemiologic Catchment Area study revealed that Cannabis use at baseline was a risk factor for the later development of depression, but depression at baseline did not predict future Cannabis use[C37]. Degenhardt[C38] found that Cannabis use was associated with mood disorder, but the association was explained by demographic factors, levels of neuroticism and use of other drugs. Three American men experienced Koro after smoking Cannabis[C39].

Suicide and Self-Harm

Borowsky[C40] in the National Longitudinal Study of Adolescent Health (USA) found that Cannabis use was a “cross-cutting” risk factor for attempted suicide in 11-17 year-olds. A rate of Cannabis dependence of 16.2% was found in adults committing DSH at a general hospital[C41]. The association was largely explained by demographic factors and other mental disorders.

C) Neuropsychological effects

Previous research is reviewed by Rogers and Robbins[C42]. Pope[C43] found deficits in word memory in heavy Cannabis users compared with controls. These persisted at 7 days, but at 28 days there were no differences in test scores. Current Cannabis users demonstrate deficits in attentional inhibition, decreased reaction time and schizotypal personality traits compared with past Cannabis users[C44] and non-users [C45].

Four studies measure cognitive impairment due to Ecstasy use. Most find that Cannabis use is not a confounding factor[C46-48], although one finds that deficits in memory, learning, word fluency, speed of processing and manual dexterity are more closely related to Cannabis use than Ecstasy[C49].

Payne reports a case of a post-head injury patient with cognitive impairment that responded to treatment of depression and Cannabis use[C50].

Auditory P50 sensory gating impairment is reported in 10 Cannabis users[C51]. Cannabis users showed changes in P300 similar to those seen in Schizotypal Personality Disorder[C52].

Decreased posterior cerebellar blood flow was found using PET in frequent Cannabis users[C53]. MRI scans of frequent Cannabis users did not differ from those of controls[C54], but Wilson[C55] found smaller whole brain and cortical grey matter volumes in subjects who started using Cannabis before age 17. Lundqvist[C56] reports decreased frontal lobe blood flow in 12 long-term Cannabis users.

D) Social harm

A review of studies measuring the effects of adolescent Cannabis use on educational achievement[C57] shows an association with poor achievement in cross-sectional studies. Prospective studies show that the association remains after controlling for a wide range of covariates. The authors suggest

the mechanism may be the adoption of an anti-conventional lifestyle. A prospective study[C58] found that Cannabis use in the USA negatively predicted college graduation. In Whites, but not Blacks, Cannabis use predicted lower family income. Marijuana use may predict or result from poor job satisfaction[C59].
Greater frequency of Cannabis use was found to be associated with some violent offences[C60], and use of various drugs, including Cannabis, increased the risk of being the victim or the perpetrator of violent behaviour[C61].
Cannabis use may result in unplanned or risky sexual encounters[C62].

Accidents

A report from The Department of the Environment, Transport and the Regions[C63] discusses the effects of Cannabis on psychomotor tasks, but concludes that it has not yet been possible to evaluate the relationship between Cannabis and accident risk. Although 4-12% of accident fatalities test positive for Cannabis, alcohol is frequently a confounding factor. Longo[C64] detected various substances in the blood of drivers in car or motorbike accidents in Australia. Cannabinoids were present in 10.8%; in 8% only THC-acid (inactive) was present, in 2.8% both THC and THC-acid were present. Fergusson and Horwood[C65] use data from a birth cohort in New Zealand to prospectively measure Cannabis use and traffic accidents. A positive association disappeared when controlled for drinking, gender and risky driving behaviours. Albery[C66] found that more than 80% of drug users drove while intoxicated, and most believed that only alcohol impaired their driving.

Tetrahydrocannabinol affects fine motor control in rats[C67], while Nabilone affects visual perception in humans[C68].

Effects of Cannabis During Pregnancy and Infancy

Data on Cannabis use was collected during the Avon Longitudinal Study of Pregnancy and Childhood[C69]. 5% of mothers smoked Cannabis before or during pregnancy. There was no increased risk of perinatal death or the need for special care, but birth weight seemed to be lower. 4.1% of pregnant women in a USA Community survey tested positive for Cannabis[C70]. Fried and Smith[C71-72] review the literature and conclude there is no evidence for reduced IQ, but a negative effect of executive function resulting from in utero exposure. A prospective study showed a relationship between prenatal exposure and various behavioural problems (hyperactivity, impulsivity, inattention) in 10 year-old children[C73].

Scragg[C74] suggested maternal Cannabis use could be a weak risk factor for Sudden Infant Death Syndrome, even after controlling for maternal smoking. Klonoff-Cohen[C75] found no increased risk with maternal Cannabis use, but did find a risk with paternal use at conception and postnatally.

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D The Gateway Theory

Alcohol and Tobacco Leading to Cannabis Use

Lewinsohn[D1] reports a prospective USA adolescent school survey investigating alcohol, tobacco and drug use. Data was collected on 3 occasions between age 14-24. Lifetime smoking increased the probability of disorders of alcohol and drug use later in life. Early onset of daily smoking increased the risk of Cannabis use disorders. Similar findings were produced from an Australian adult community survey[D2]. Durant[D3] found that early cigarette smoking was the strongest correlate of various risky health behaviours in adolescence, including use of Cannabis. Johnson[D4] found that adolescent smokers and drinkers were more likely to indicate they would use drugs in the future than controls, with smokers showing a stronger effect than drinkers. Golub[D5] described 3 stages in drug progression in adolescents interviewed at 3 year intervals: alcohol/tobacco, Cannabis, hard drugs. Scheier[D6] describes a school survey among USA adolescents and confirms the importance of early tobacco and alcohol use as a gateway to Cannabis use. The role of a prevention programme in altering progression of drug use is investigated.

Willner[D7] used a self-report questionnaire in UK secondary schoolchildren to show that positive expectancy of alcohol use predicted positive expectancy of Cannabis use and measures of problem drug use. Jones[D8] reported that USA students who binge drank were more likely to use Cannabis.

Cannabis Leading to the Use of Other Drugs

Strang, Witton and Hall discuss the gateway theory in a BMJ review[D9]. Fergusson and Horwood[D10] present important longitudinal data from a birth cohort in New Zealand. Cannabis use significantly predicted future use of hard drugs, and the effect was still seen after adjustment for covariate factors. The authors conclude that their data are consistent with the theory that Cannabis acts as a gateway to hard drugs. It was also found in an Australian community survey that Cannabis use was associated with use of and dependence on other drugs[D11]. Golub and Johnson[D12] present interesting data from the National Household Survey on Drug Abuse (USA). They suggest that the rate of progression to Cannabis and hard drugs may have altered during the last century, being uncommon in those born before WW2, peaking in those born in the 1960s, and declining in those born since 1970. Merrill[D13] find that marijuana use predicted use of other drugs, even following correction for other risky behaviours. Pederson and Skrondal[D14] describe a sequence of drug initiation as follows: Alcohol, Cigarettes, Cannabis, Amphetamines, Ecstasy, Heroin. Zinkernagel[D15] found a similar pattern of initiation of drugs among heroin addicts. Haas and Peters[D16] and Kane and Yacoubian[D17] both find rapid progression through the drug sequence among offenders. Pacula[D18-19] presents a model of progression through a sequence of drug initiations, and discusses economic effects and implications of drug treatment programmes.

Pharmacological Studies Supporting Gateway Theory

Evidence relevant to the gateway theory comes from studies reporting the interactions between various substances when used together. Lukas and Orozco[D20] described enhanced effects of Cannabis and higher plasma delta-9-THC levels after drinking alcohol. Reid and Bornheim[D21] from studies on mice showed that both Cannabidiol and delta-9-THC increased the brain levels and behavioural response to some drugs of abuse (Cocaine and PCP) but not others (Morphine, Methadone, MDMA). Lamarque[D22] studied the effects of chronic delta-9-THC administration to rats, and found that the locomotor response to Heroin and Amphetamine was potentiated.

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E Cannabis and the Law

UK

The British Medical Journal invites experts to argue the case for and against decriminalisation of Cannabis[E1]. The UK Medicines Control Agency was criticised for insisting on full toxicology testing of Cannabis extracts in clinical trials, despite accumulated knowledge of the drug's safety[E2-E3]. A case is reported of a man found not guilty of cultivating and supplying Cannabis after pleading the defence of necessity. He used the drug to relieve pain from a spinal injury, and gave it to two people with MS[E4].

The British Journal of Psychiatry reviews "Drugs: Dilemmas and Choices" by a Working Party of the Royal College of Psychiatrists and the Royal College of Physicians (Crown and Lee, London: Gaskell)[E5].

USA and Canada

Dinardo[E6] analyses the impact of increases in minimum drinking age in various states of the USA, and find that a decreased prevalence of alcohol consumption was balanced by an increase in Cannabis consumption. Farrelly[E7] reviews similar evidence, and uses data from the National Household Survey on Drug Abuse (1990-96) to conclude that higher fines and a higher probability of arrest for possession of Cannabis decrease the probability of use among adolescents, and higher cigarette taxes also deter use. Clark[E8] argues that physicians should have the right to prescribe Cannabis to patients who may benefit from it. Experts from the Centre for Addiction and Mental Health[E9] reviewed proposals in Ontario, Canada, to use drug testing for welfare recipients. They concluded the proposals were inadvisable on ethical, scientific and economic grounds. Canada introduced regulations allowing patients to apply for the medical use of Cannabis[E10-E11] although users would be required to carry ID cards[E12].

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F International Comparisons

Reviews

MacCoun and Reuter examine alternative legal regimes for controlling Cannabis availability and use[F1]. They favour a model of depenalised possession and personal cultivation, rather than outright legalisation.

The Netherlands

The Annual Report for 2001 of the Dutch National Drug Monitor[F2] concluded that the trend for increasing numbers of consumers of Cannabis among the young was levelling off, or even decreasing. Rates of Cannabis use were lower throughout Europe than in the USA and Australia, and the highest prevalence in Europe was in England and Wales. The rate of use in secondary schools in the Netherlands increased between 1988 and 1996, but levelled off in 2000 with a trend downwards. The demand for outpatient treatment for Cannabis problems increased through the 1990s in the Netherlands, but had levelled off by 2000. The number of "coffee shops" had decreased by 32% since 1997.

Other Countries

Hall[F3] analyses Australian Cannabis policy and weighs up the harm resulting from Cannabis use, and the less tangible harm resulting from its prohibition. He concludes that a trade-off between these competing forces have resulted in a solution that continues to prohibit Cannabis use, but reduces the severity of penalties by decriminalisation or diverting offenders towards treatment and education. The same author[F4-F5] summarises the report of the Working Party on the Medical Uses of Cannabis in New South Wales, Australia. This report concluded that smoked Cannabis would be unlikely to be available on prescription in Australia because of difficulties with the registration process, so any prescribed Cannabis derivatives would need to be natural or synthetic drugs. It recommended that patients with certain disorders could receive medical certification that would allow them to cultivate and use small amounts of cannabis without the risk of prosecution.

Reuter[F6] laments the failure of USA drug policy to take account of research evidence. A leading article in The Lancet Oncology supported the use of immunity from prosecution on humanitarian grounds for terminally ill patients using Cannabis. The BMJ[F7] reports a proposal from the Catalan parliament to legalise the use of Cannabis for therapeutic purposes.

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G Therapeutic Uses of Cannabis

A number of journals have featured reviews of the therapeutic uses of Cannabis during the past two years. Pertwee[G1] describes advances in the understanding of the pharmacology of the CB1 and CB2 receptors, and clinical applications of agonists and antagonists. Robson[G2-G3] presents findings from a review of the scientific literature commissioned by the Department of Health. He concludes that cannabinoids may provide novel treatment options in disorders where current treatments are unsatisfactory, including neurological conditions, AIDS, cancers, anxiety, insomnia and epilepsy, and may also be useful as anti-emetics, analgesics and in reducing intra-ocular pressure. In the Archives of General Psychiatry, Watson, Benson and Joy summarise the 1999 Institute of Medicine report "Marijuana and Medicine: Assessing the Science Base"[G4-G5]. This report, funded by the Office of National drug Control Policy (USA) called for heavier investment in biological research, careful clinical studies, analysis of psychological effects and evaluations of the health consequences of heavy Cannabis use. It recommended against the use of smoked Cannabis in medicine and recommended consideration for the compassionate use of Cannabis. It evaluated the abuse potential, tolerance, withdrawal and gateway risks of the medical use of cannabinoid drugs.

The British Medical Journal published systematic reviews of the literature for the use of cannabinoids as analgesics and anti-emetics. Campbell[G6] found that cannabinoids were no more effective than Codeine as analgesics, and had CNS depressant effects that limited their use, and concluded "their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used". Further studies were needed for spasticity and neuropathic pain. Tramer concluded "in selected patients, cannabinoids … may be useful as mood-enhancing adjuvants for controlling chemotherapy-related sickness", but feared that potentially serious adverse effects were likely to limit their widespread use[G7]. These were dizziness, dysphoria, hallucinations, paranoia and hypotension. A double-blind, randomised, placebo-controlled crossover study using the synthetic cannabinoid Nabilone showed no significant reduction in dystonia[G8]. The BMJ reported the world's largest clinical trial of Cannabis, into the control of pain and tremor in MS[G9]. The Journal of Cannabis Therapeutics contains a review of the role of Cannabis in patients with HIV disease[G10], data on the efficacy of smoked Cannabis in controlling chemotherapy-induced nausea[G11], and a case series describing various medical patients who have benefited from the drug[G12].

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H Treatments/Prevention of Cannabis Use

Prevention/Public Health

Botvin[H1] reviewed school-based prevention approaches for drug use, and found a large gap between evidence-based methods and what was generally available in schools. "The most promising approaches target … the beginning of adolescence and teach drug resistance skills and norm setting either alone or in combination with general personal and social skills". Schinke[H2] developed and tested skills- and community-based approaches to prevent substance abuse among Native American schoolchildren. Over 3.5 years, Cannabis use was lower for those who learned cognitive and behavioural skills for substance use prevention, while an intervention engaging local community residents in reducing substance use appeared to have no benefit. Palmgreen[H3] found that televised public service announcements were effective at reducing substance use among sensation-seeking adolescents. The effectiveness of a Dutch school-based drug prevention programme was tested by comparing students at schools who did and did not participate in the programme[H4]. The programme improved knowledge about drugs, but did not seem to influence attitudes.

Treatment of Cannabis Dependence

An Editorial in Addiction[H5] discussed UK Department of Health guidelines and found them to be "enormously useful". Weisner [H6] found that an integrated package of medical and substance abuse care was effective for patients with substance-abuse related medical conditions, although the patients studied were not specifically Cannabis abusers. Copeland[H7] found that both 1 session and 6 sessions of CBT were more effective than waiting list treatment in promoting abstinence and reducing Cannabis–related problems in Australian adults (N=229) who wished to stop using Cannabis. Stephens[H8] carried out a randomised controlled trial of psychological interventions for USA adult Cannabis users seeking treatment (N=291). It showed that a 14-session CBT programme and a 2-session motivational interview were both more effective than waiting list at reducing Cannabis use and dependence up to 16-month follow-up. The two programmes were equally effective. Winters[H9] offered a 12-step programme (Minnesota Model) to USA adolescents (N=245) with substance use disorder. Cannabis was the most commonly used drug at intake. The study compared treatment completers with dropouts and waiting list controls, and found that 12-month abstinence was significantly higher in treatment completers than in both of the other two groups.

A double-blind, placebo-controlled crossover study of USA Cannabis users (N=10) found that Bupropion was not effective at reducing symptoms of Cannabis withdrawal, but made them worse[H10]. Injection of Lithium prevented cannabinoid withdrawal syndrome in rats, an effect thought to be mediated by oxytocinergic neural activation[H11].

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I Factors Leading to Harmful Cannabis Use

Factors Leading to Cannabis Use

A large longitudinal community study (Early Developmental Stages of Psychopathology, N=3021) in metropolitan Munich measured risk factors for Cannabis use, and progression to regular use[I1]. A cumulative logistic regression model was used to estimate associations. Significant factors included family history of substance use disorder, low self-esteem and competence, lack of commitment to not using drugs, immediate availability of drugs, peer group drug use and previous history of nicotine dependence and alcohol use disorders.

Little biological research has been published recently. Miles[I2] examined various risk-taking behaviours in a study of adolescent twin pairs. For Cannabis use, genetic and environmental factors were equally important. Genetic factors are thought to be mediated via impulsive and risk-taking personality traits. Another twin study[I3] measured concordance of abuse and dependence of various drugs. Marijuana dependence had the highest prevalence of dependence for any drug. Marijuana abuse had some unique genetic factors, and was more influenced by family environmental factors than other drugs.

Personality factors generally relate to impulsivity and sensation-seeking. Dervaux[I4] found that in patients with Schizophrenia the personality variables predictive of Cannabis use are the same as those in the general population. Brook[I5] used data from a longitudinal adolescent cohort study to derive personality traits predictive of Cannabis use. A latent variable was discovered, termed unconventiality, and this included a high score for rebelliousness and low scores for responsibility and intolerance of deviance. This trait has been shown to be the only one that is strongly associated with Cannabis use[I6]. White[I7] found that various measures of adolescent psychopathology (including ADHD, conduct disorder and violence) predicted higher levels of Cannabis use. A prospective longitudinal survey found a strong association between early conduct problems and Cannabis initiation, and early smoking was also predictive[I8]. A study of Icelandic teenagers showed that the presence of antisocial behaviour aged 14 predicted initiation of Cannabis use before the age of 17[I9].

Other psychological variables have been shown to influence use of Cannabis. Wills[I10] found that from a range of variables, low scores for behavioural coping and high scores for disengagement (anger coping, helpless coping and hangout coping) predicted use of various substances. In a paper on time perspective, Wills[I11] found that future orientation was inversely related and present orientation was positively related to substance use. One survey of USA high school students found that low life satisfaction was correlated with a higher incidence and earlier onset of use of various substances including Cannabis[I12], and another implicated personality factors such as high anxiety sensitivity in those who conformed in their use of Cannabis[I13]. Cannabis use was found in a questionnaire study to correlate with schizotypal personality traits in French students[I14], and a UK study showed similar findings[I15].

Psychological motivations for using Cannabis were studied by Linkovich-Kyle[I16]. Heavy users had positive expectancies of relaxation, cognitive enhancement and social facilitation. Boys[I17] found in a cross-sectional survey that negative effects of substance use did not correlate with patterns of use, whereas there was a correlation with the perceived benefits. A survey of poly-drug users[I18] rated the most popular reasons for using drugs. These were relaxation, intoxication, stimulation, enhanced activity and relief from depressed mood.

Various social factors influence Cannabis use. The effect of a range of psychosocial factors on use of alcohol, cigarettes and Cannabis was measured in USA adolescents[I19]. The only significant variable was social support, as adolescents with higher levels of social support were more likely to abstain. Boyle[I20] found only a modest concordance within families between siblings, but concluded that the dominant influence within families was from older siblings, not parents. A study of family structure and drug use in UK and French adolescents found a broadly similar picture in the two countries[I21]. Children from non-intact families,

those who were dissatisfied with their parents, and those who were not supervised were more likely to use drugs. A cross-sectional survey of USA high school students[I22] found that peer social influences affected use of Cannabis, but parental influences did not. Among the sons of fathers with substance use disorders, Clark[I23] found that Cannabis use was predicted by early tobacco use, minority ethnicity and conduct disorder. Having a parent with an alcohol problem was shown to relate to earlier drug use among USA adolescents[I24]. A Finnish longitudinal survey of adolescents[I25] identified male gender, absence of mother, frequent lack of interest and early age at first sexual intercourse as relating to early Cannabis use. Various risk factors for substance use, including peers' risk behaviours (suicidality, deviance and substance use), family factors and individual psychopathology had a multiplicative influence on risk[I26]. Ellickson[I27] also identified early smoking and experimentation as a risk for Cannabis use. Kosterman[I28] suggested that peer groups influenced early Cannabis and alcohol use, but that proactive parenting could delay initiation.

Factors Leading to Cannabis Dependence

A USA Twin Register study (N=1198 pairs)[I29], rated abuse of and dependence on various illicit substances including Cannabis. The odds ratio for concordance for Cannabis dependence was 12.4 for MZ and 2.4 for DZ twins. Genetic and environmental factors appeared to be equally important, in contrast to dependence on most other substances, where genetic factors were predominant.

Bierut[I30] recruited subjects with Alcohol dependence (N=1212) and their siblings (N=2755). Rates of Cannabis dependence were greater in siblings of subjects than in siblings of controls. Cannabis dependence was found in siblings of subjects who also had a diagnosis of Cannabis dependence, suggesting that both common and substance-specific addictive factors are present in families.

DeWit[I31] measured factors correlating with a diagnosis of Cannabis use disorder in a Canadian community sample (N=2729). Early and frequent use were associated with the development of dependence. The results suggested a threshold of number of uses associated with an increased risk of developing dependence (100-199 in males, 50-99 in females). Data from the Australian National Survey of Mental Health and Wellbeing showed a significant association between current tobacco use and Cannabis dependence[I32].

Orford[I33] describes excessive appetite as a model for dependence on various substances. Conway[I34] found that low scores for "Constraint" predicted dependence among users of various drugs in a USA family study.

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J The Biology of Cannabis

Animal Studies

The role of Cannabis in inhibiting learning and memory has been investigated in several studies of the rat hippocampus. The effects of cannabinoid receptor agonists on forskolin-induced formation of new synapses between rat hippocampal neurones in culture were examined[J1]. Inhibitory effects were observed, and were reversed by a selective CB1 receptor antagonist. Nava[J2] found that rats did not become tolerant to the effects of chronic (2 weeks) administration of delta-9-THC on hippocampal ACh concentration, or on the altered performance in the T maze. The effects seemed to be independent in time of onset, and both were blocked by CB1 receptor antagonists. Lawston[J3] demonstrated morphological changes in the rat hippocampus following chronic administration of WIN 55,212-2, a synthetic CB1 receptor agonist. The changes were similar to those seen after ischaemic or toxic damage.

Interactions have been observed between cannabinoids and other neurotransmitter systems. Dynorphin-deficient mice do not show negative motivational effects with tetra hydrocannabinol, suggesting that these effects are mediated by endogenous opioids[J4]. Endogenous opioid receptors were also shown to be implicated in modulating reward pathways for repeated THC administration[J5]. Repeated exposure to THC induces behavioural sensitisation not only to cannabinoids, but also to opioids in rats[J6]. Co-administration of nicotine facilitates the acute response to THC in mice, and also enhances tolerance and dependence[J7]. Hoffman and Lupica[J8] suggest from their studies of the rat hippocampus that presynaptic CB1 receptors reduce GABA-A but not GABA-B mediated synaptic inhibition of CA1 pyramidal neurones. Administration of cannabinoid receptor agonists decreased adrenaline secretion from the adrenal medulla in rabbits, an effect that was probably mediated by presynaptic CB1 receptors[J9]. Ventral tegmental and substantia nigra dopaminergic neurones in rats develop a differential response to delta-9-THC following chronic cannabinoid exposure, and this could be an explanation for the observation that humans develop tolerance to many of the physiological effects of Cannabis, but not its euphorigenic actions[J10].

Several articles discuss progress in research into endogenous cannabinoids. It was shown that they could facilitate retrograde communication across hippocampal synapses to modulate GABA release[J11]. Christie and Vaughan[J12] proposed that anandamide and 2-arachidonylglycerol are the key endocannabinoids involved in this process, and The Lancet[J13] reported anandamide as being a probable mediator of the analgesic effects of the endocannabinoid system.

Mice bred without the CB1 receptor show behavioural effects similar to those seen in Cannabis intoxication and dopamine D2 activation, and it has been suggested that this could provide a model for schizophrenia[J14].

The Pharmacology of Cannabis in Humans

A CB1 receptor antagonist (SR141716) administered orally to 63 volunteers blocked the physiological and mood-altering effects of inhaled Cannabis[J15]. Naltrexone did not block the effects of THC, suggesting that they are not mediated via opioid receptors[J16]. Inhaled THC increased tolerance to pain in regular Cannabis smokers, and the effects were not blocked by Naltrexone[J17]. Co-administration of alcohol and THC in healthy volunteers caused an increase in plasma THC levels and potentiated the effects on mood[J18].

Postmortem brain tissue from individuals with Schizophrenia, some of whom smoked Cannabis, were compared with controls[J19]. There was an increase in radioligand binding to CB1 receptors in the dorsal prefrontal cortex in Schizophrenia, and an increase in the density of receptors in the caudate-putamen in response to recent ingestion. Chambers reviews recent research into the neuropathology of Schizophrenia, and suggest that a dysregulation of

dopamine and glutamate signalling in the nucleus accumbens may cause the increased risk of comorbid substance abuse[J20].

Neuroimaging

PET scanning was used to study regional blood flow in Cannabis users performing an auditory attention task, before and after smoking Cannabis[J21]. After smoking, blood flow increased in a number of paralimbic brain regions (orbitofrontal lobes, insula, temporal poles), and in the anterior cingulate and cerebellum. Blood flow decreased in temporal lobe regions sensitive to auditory attention effects. Voruganti[J22] reports a case of a patient with Schizophrenia who surreptitiously smoked Cannabis during a SPECT study of dopaminergic function in the brain. There was an immediate 20% decrease in striatal D2 receptor binding, indicating increased synaptic dopamine activity.

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K Testing for Cannabis

Methods of Analysis

Klein reviews the importance of hair analysis of various drugs of abuse, and concludes that this method provides greater information than blood, urine or saliva testing[K1]. The hair of Spanish university students was tested for Cannabis, Cocaine and Amphetamine, but the number of false positives obtained with a method of Cannabis testing (RIA) made it unsuitable for routine use[K2]. Ostrea[K3] compared maternal interview, maternal hair analysis and meconium analysis in detecting perinatal exposure to cocaine, opiates and Cannabis. Maternal interview had the highest sensitivity in detecting Cannabis exposure (but the lowest for the other drugs), but hair and meconium analysis had low sensitivity (high for other drugs).

Kintz[K4] piloted a method for the measurement of delta-9-THC in sweat and saliva samples taken from injured drivers. The samples were easy to obtain, but the test was less sensitive than urine sampling, because of lower concentrations of the drug in these fluids. Weinmann[K5] reports an improved method for the detection of various cannabinoids in urine samples. ElSohly[K6] demonstrates that the presence of a particular metabolite in the urine discriminates between users of Marinol and Cannabis. Giroud[K7] proposes a mathematical model that could allow an estimation of the time of exposure to Cannabis by comparing various metabolites in plasma. Fucci[K8] suggested salivary sampling using the EPITOPE device as an alternative to blood sampling where this is prohibited. Akinci[K9] found a significant discordance (13%) between reported Cannabis use and that detected by urine sampling in a survey of 200 adolescents.

Ethical and Political Implications

Verstraete and Pierce[K10] review recent trends in workplace drug testing, and report the formation of the European Workplace Drug Testing Society to oversee testing in different countries. Steinmeyer[K11] reports the use of roadside drug testing using urine, sweat or saliva samples by police in Germany. The tests were followed up by blood testing, and it was found that the roadside tests gave correct results in 97% of cases. Leson[K12] investigated concerns that ingested hemp products could cause false positive urine tests for Cannabis, but found that at doses commonly ingested this was not a problem.

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