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problematic behaviours. They concluded that "Available evidence does not support an important causal relation between cannabis use and psychosocial harm, but cannot exclude the possibility that such a relation exists".

Whatever the nature of the association, it seems clear that long-term heavy cannabis use carries a variety of negative attributes. A case control study compared 108 heavy-use long-term cannabis users, who had on average smoked 18 000 times, with 72 age-matched controls who had smoked cannabis <50 times [18••]. The heavy-use cannabis smokers reported significantly lower educational attainment and lower income than did controls. When asked to rate the subjective effects of cannabis on cognition, memory, career, social life, physical and mental health and various quality-of-life measures, a large majority of heavy-use cannabis smokers reported negative effects of their drug use.

Cannabis and substance dependence

Although it was previously thought that cannabis was not a drug of addiction, it is now recognized that cannabis use can lead to substance dependence in perhaps as many as 10% of regular users, according to the internationally accepted DSMIV definition of 'substance dependence' [6•]. In both animals and humans, a clear withdrawal syndrome can be identified [6•]. In rodents, chronic administration of THC or synthetic cannabinoids leads to downregulation and desensitization of cannabinoid CB_1 receptors in the brain [19]. This might partly explain the tolerance that develops in both animals and humans on repeated use of the drug. In regular cannabis users, abstinence leads to a withdrawal syndrome characterized by negative mood (irritability, anxiety, misery), muscle pain, chills, sleep disturbance and decreased appetite. A placebo-controlled study showed that these symptoms were significantly reduced by oral administration of THC, suggesting that the withdrawal syndrome and underlying substance dependence were related to effects of THC on the cannabinoid CB_1 receptor, rather than to any other component of herbal cannabis [20].

Other potentially toxic effects of long-term cannabis use

Some of the most serious adverse effects of smoked cannabis are on the respiratory system. Although little progress has been made recently in quantifying such risks, warnings continue to be issued about the potential for long-term damage or even malignancy in the airways [21]. It is known that lung macrophages isolated from cannabis smokers exhibit impaired anti-bacterial activity, and one experimental study showed that this might be caused, in part, by reduced expression of inducible nitric oxide synthase and decreased production of nitric oxide [22]. A review of the evidence for immunosuppressant effects of cannabis concluded that, with the exception of the effects of cannabis smoking on broncho-alveolar immunity, there is no evidence that cannabis causes any other serious immunosupression in users [23]. The authors suggested that the effects on lung macrophages might be related to the ability of cannabis in animal studies to cause a shift from Th1 to Th2 cytokine production.

With increasing use of cannabis, there remains a concern that cannabis use during pregnancy might impair foetal development. Reviews of data from humans, however, suggest that such effects are minimal for cannabis users when compared with the well-documented adverse effects of tobacco or alcohol use [24,25•]. Nevertheless, treatment of pregnant rats with high doses of THC did lead to significant reductions in expression of neural adhesion molecule L1 in the foetal brain — a key protein for brain development [26].

Conclusions

A review of the literature suggests that the majority of cannabis users, who use the drug occasionally rather than on a daily basis, will not suffer any lasting physical or mental harm. Conversely, as with other 'recreational' drugs, there will be some who suffer adverse consequences from their use of cannabis. Some individuals who have psychotic thought tendencies might risk precipitating psychotic illness. Those who consume large doses of the drug on a regular basis are likely to have lower educational achievement and lower income, and may suffer physical damage to the airways. They also run a significant risk of becoming dependent upon continuing use of the drug. There is little evidence, however, that these adverse effects persist after drug use stops or that any direct cause and effect relationships are involved.

In contrast, cannabis might have beneficial effects in some medical indications. There is considerable literature obtained from animal studies to suggest that cannabis has analgesic effects [27]. Until recently, however, there has been a dearth of controlled clinical studies to validate such effects in patients. This has now changed, with the publication in the past two years of a number of double-blind placebo-controlled trials showing the effectiveness of cannabinoids in relieving chronic neuropathic pain [28,29] or pain associated with multiple sclerosis [30••, 31]. The largest of these trials involved 630 multiple sclerosis patients and showed significant pain relief after 15 weeks of treatment with either pure THC or cannabis extract [30]. It seems likely that medicinal cannabis will re-enter the Pharmacopoeia.

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"The good and the bad effects of trans-delta-9-tetrahyrdocannabinol on humans"

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Review

The good and the bad effects of (−) *trans*-delta-9-tetrahydrocannabinol (Δ^9-THC) on humans

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Abstract

This review analyses the therapeutic usefulness of Δ^9-tetrahydrocannabinol and its potential to induce adverse reactions on humans. During the last 30 years an enormous amount of research was carried out resulting in the disclosure of the cannabinoid system in Central Nervous System, with its CB_1 and CB_2 receptors, and the agonist anandamide. Under the clinical point of view, Δ^9-THC produces some therapeutic benefits which are beyond reasonable doubt. Thus, the effects on nausea/emesis due to cancer chemotherapy, as appetite promoter, on some painful conditions and on symptoms of multiple sclerosis are clearly demonstrated.

Δ^9-THC is not devoid of ill effects. On the cognitive domain it impairs the human capacity to discriminate time intervals and space distances, vigilance, memory and the performance for mental work. On the psychic area Δ^9-THC may induce unpleasant reactions such as disconnected thoughts, panic reactions, disturbing changes in perception, delusions and hallucinatory experiences. However, the long term effects on the psyche and cognition are not known as there are no reports of prolonged use of Δ^9-THC. Actually, it has been proposed by WHO that Δ^9-THC should be rescheduled to schedule IV of the United Nations Convention on Psychotropic Drugs, as it does not constitute a substantial risk to public health and its abuse is rare if at all.

Keywords: Δ^9-THC; Dronabinol dependence; Abstinence; Multiple sclerosis; Nausea and vomiting; Appetite promoter

Contents

In an interesting review article on the history of cannabis use as a medicine—*The Forgotten Medicine*—by Aitken and Mikuriya (1980), two quotations deserve attention: "in 1890 Dr J. Russel Reynolds, Physician in Ordinary to Queen Victoria wrote: Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess;" and "quote from the Egyptian Government's Annual Report on Narcotics, 1944: Cannabis is a thoroughly vicious drug, deserving the odium of civilized people"

Very few drugs, if any, have such a tangled history as a medicine. In fact, prejudice, superstition, emotionalism and even ideology have managed to lead cannabis to ups and downs concerning both its medicinal properties and its toxicological and dependence-inducing effects. However, several breakthroughs occurred during the last 50 years and, consequently, the situation is now settled, at least partially, in that cannabis and its main active principle Δ^9-THC may actually be valuable medicines and the plant cannabis is not a 'thoroughly vicious drug'.

Delta-9-tetrahydrocannabinol, or 6a, 7, 8, 10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]-pyran-1-ol, is a substance possessing several stereochemical variants. One of them is (−)-*trans*-delta-9-tetra-hidrocannabinol, also called dronabinol or Δ^9-THC.

It was isolated, identified and synthesized in the 1960s (Gaoni and Mechoulam, 1964). The identification of several other cannabinoid compounds were also achieved in

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the following years. Among them the isomer Δ^8-THC which is, however, less potent than Δ^9-THC (Karniol and Carlini, 1973).

Almost three decades later, cannabinoid receptors in the brain were described (for reviews see Howlett, 1995; Childers and Breivogel, 1998; Pertwee, 1997, 1999), their cloning were achieved (Rinaldi-Carmona et al., 1996) and anandamide, the endogenous cannabinoid, was isolated and identified (Devane et al., 1992; Mechoulam et al., 1998a; Martin et al., 1999). Several analogs of anandamide were synthesized and structure-activity relationships were established (Mechoulam et al., 1998b).

All accomplishments concerning the chemistry of marihuana constituents and the description of an endogenous cannabinoid system were accompanied by a great deal of research on cannabinoid pharmacology and opened up opportunities to resume clinical research with these substances, mainly Δ^9-THC.

1. Beneficial effects (therapeutic effects) of Δ^9-THC

Much of the research carried out more recently in several countries dealt with old therapeutic folk uses of marihuana (Consroe et al., 1975; Mechoulam and Carlini, 1978; Mechoulam et al., 1984), such as the possible anti-epileptic and hypnotic properties of Δ^9-THC and cannabidiol, the latter a non-hallucinogenic cannabis constituent (Cunha et al., 1980; Carlini and Cunha, 1981). Other therapeutic indications such as anti-emetic, as antispasmodic, as analgesic, in glaucoma, as hypnotic, in asthma, in epilepsy, as appetite stimulant, as anxiolytic, and in Tourette syndrome, deserved also pre-clinical and clinical studies (Nakano et al., 1978; Ilaria et al., 1981; Musty, 1984; Sethi et al., 1986; Ashton, 1999; Ashton, 2001; Williamson and Evans, 2000; Söderpalm et al., 2001; Robson, 2001; Müller-Vahl et al., 2002).

For a few therapeutic indications Δ^9-THC produce beneficial clinical results that are beyond reasonable doubt (for review articles see Formukong et al., 1989; Mechoulam et al., 1998a; Williamson and Evans, 2000; Robson, 2001; Grotenhermen and Russo, 2002; Iversen, 2003). In the present review article four of them will be approached, namely, the (Δ^9-THC) effects on nausea/vomiting, on appetite, on pain and on symptoms of multiple sclerosis.

One such clinical indication refers to the anti-emetic effect in cases of chemotherapy-associated nausea and emesis. The first randomized, double-blind placebo-controlled trial was that of Sallan et al. (1975) showing that Δ^9-THC was more effective than placebo in controlling nausea/vomiting of cancer patients receiving chemotherapy. The control of emesis afforded by Δ^9-THC far exceeds that provided by prochlorperazine (Orr et al., 1980); it abolishes totally or partially the nausea and vomiting refractory to standard anti-emetic agents in 72% of patients (Lucas and Laszlo, 1980).

Poster et al. (1981) reviewed seven well-controlled studies on the subject; in six of them Δ^9-THC was a superior anti-emetic compared to control agents. These authors also concluded that toxic effects were manageable and suggested that THC use represents a major advance in anti-emetic therapy. In a more recent review (Tramèr et al., 2001) on the anti-emetic effect of cannabis compounds, involving 1366 cancer patients participating in 30 randomized studies, it was shown that cannabinoids act slightly better than alizapride, chloropromazine, haloperidol, domperidone, metoclopramide, prochlorperazine and thiethylperazine in crossover trials. These patients selected cannabinoids for future chemotherapy (Tramèr et al., 2001). Very successful treatment for nausea and vomiting was also reported by Musty and Rossi (2001). These authors examined the reports obtained from six American States, which conducted clinical trials on 748 cancer patients who smoked marihuana, and 345 patients who used oral Δ^9-THC. Both treatments promoted, respectively, 70–100% and 76–88% relief from nausea and vomiting.

The beneficial effects of Δ^9-THC on nausea/vomiting are partially counterbalanced by the adverse reactions reported by the patients such as drowsiness, apprehension and anxiety, dry mouth, etc. It is possible that such undesirable side effects may be minimized by simultaneous administration Δ^9-THC and cannabidiol, as observed in healthy subjects (Karniol et al., 1974; Zuardi et al., 1982).

Another clinical indication that is well established refers to the appetite promoter effect of marihuana and of cannabinoids (Hollister, 1971; Mechoulam and Carlini, 1978; Mattes et al., 1994). It is a clinical fact that HIV patients are prone to severe weight loss due to anorexia (Clebowski et al., 1989); Δ^9-THC improved appetite in these patients, and consequently brought also a betterment of their nutritional status and of other symptoms such as improving mood and decreasing nausea (Struwe et al., 1993; Beal et al., 1995, 1997). The anorexia-cachexia associated with cancer may also be counteracted by Δ^9-THC (Ekert et al., 1979; Gorter, 1991; Plasse et al., 1991). In fact, the promotion of appetite in marihuana smokers is a well-known fact (Foltin et al., 1988); therefore it is not surprising that Δ^9-THC has been considered as an effective appetite stimulant drug in cancer patients (Regelson et al., 1976).

An interesting corollary of these findings is the recent demonstration of the potent anorectic effect in obese animals of the substance SR 141716, an antagonist of the cannabinoid receptor CB_1 (Colombo et al., 1998; Mechoulam and Fride, 2001; Cota et al., 2003; Vickers et al., 2003).

It has also been shown in rats that cannabinoid antagonists may prevent the relapse of cocaine use (De Vries et al., 2001; Piomelli, 2001) and the self-administration of methamphetamine (Vinklerová et al., 2002).

According to Grotenhermen (2002a) the effects of cannabinoids on painful conditions of several aethiologies are relatively well confirmed. In fact, several recent review articles analysed anedoctal reports and controlled clinical trials on the analgesic effect of Δ^9-THC and other cannabinoids in painful conditions such as cancer, damaged nerves, migraine, post-operative pain, spinal cord injury, dental pain, phantom limb pai etc. (Noyes et al., 1975; Formukong et al., 1989; Ashton, 1999; Williamson and Evans, 2000; Robson, 2001; Holdecroft, 2002; Vaughan and Christie, 2002). The very ancient use of marihuana smoking as a headache and migraine medicament, reviewed by Russo (1998, 2001), adds support to the contention that Δ^9-THC and other cannabinoids are indeed active in alleviating pain.

In general, all the reports and trials analysed in the above mentioned reviews acknowledge that Δ^9-THC does indeed have analgesic properties which, according to some authors, approximately matches that of codeine. However, side effects such as sedation, dizziness, ataxia, blurred vision, tachycardia, psychological disturbances as anxiety and fear near panic states, may limit its use. Nevertheless, it also should be taken into consideration that these side effects are not life threatening as those from opiates, which also produce an array of adverse reactions.

Recently, Campbell et al. (2001) reviewed 20 randomized control led trials, nine from those being analyzed; a total of 222 patients participated in five trials on cancer pain, two on postoperative pain and two on chronic non-malignant pain. They concluded that the analgesic effects of cannabinoids were as effective as 50–120 mg of codeine.

The effects of *Cannabis sativa* L. on muscle spasticity, tremors, and neuropathic pain are known since at least the 19th century; in fact, famous physicians of that time, such as W. O'Shaughnessy in India and J.R. Reynolds in England (the personal physician of Queen Victoria), were enthusiastic prescribers of Indian Hemp (Aitken and Mikuriya, 1980; Robson, 2001; Grinspoon and Bakalar, 1993). Near 150 years later, Consroe et al. (1997), through interviews with 112 multiple sclerosis (MS) patients, confirmed the striking improvement (according to the patient's reports) afforded by cannabis smoking on MS symptoms such as the relief of chronic pain, night-time spasticity, tremor, impaired balance and trigeminal neuralgia associated with the disease.

Results obtained with clinical trials employing Δ^9-THC in MS patients are consistent with the claims of the Consroe's respondents (1997). Thus, Petro and Ellenberger (1981); Clifford (1983); Ungerleider et al. (1987); Meinck et al. (1989); Maurer et al. (1990); Brenneisen et al. (1996), reported that MS patients receiving Δ^9-THC presented improvements in tremor, ataxia, spasticity, nocturia and in well-being; adverse reactions as disphoria, headache, dry mouth, a 'high' sensation were also described.

On the other hand, at least two studies did not confirm these beneficial effects. In one of them (Killenstein et al., 2002) Δ^9-THC not only was unable to reduce spasticity, but also worsened the MS patients global impression; Greemberg et al. (1994), on the other hand, found that marihuana smoking further impaired the posture and balance in MS patients.

However, any possible doubts that might exist on whether or not Δ^9-THC is an useful medicine for MS symptoms, were removed by the results obtained in four very recent randomized, double-blind, placebo-controlled trials (Anonymous, 2002a, b). In these studies, 344 patients suffering from MS and neuropathic pain received a cannabis extract containing Δ^9-THC and cannabidiol (CBD) as its principal components; the medicine was delivered by mean of a spray into the mouth. The four studies evaluated the effects of the Δ^9-THC/CBD mixture on, respectively; neuropathic pain (66 patients), chronic refractory pain due to MS (70 patients), general symptoms of MS (160 patients), and pain due to brachial plexus injury (48 patients). In all the four studies a statistically significant improvement in the symptomatology and an excellent safety profile were obtained which could in part be due to the self-titration of the dose by the patients (Anonymous, 2002b). A first detailed study on this striking beneficial effect of Δ^9-THC/CBD mixture on the multiple sclerosis symptomatology has been published very recently (Wade et al., 2003): 24 patients obtained great relief from pain; bladder control, muscle spasms and spasticity were also improved. Side effects were predictable and well tolerated.

This lack of side effects could also be due to fact that cannabidiol is able to block anxiety and other ill effects of Δ^9-THC (Karniol et al., 1974). In conclusion it can be said that the statement by Drs Hare and Chrystie (1892) more than 100 years ago ('Cannabis is very valuable for the release of pain, particularly that depending on nerve disturbances; it produces sleep, it gives great relief in paralysis and tends to quiet tremors...') was finally proved to be correct.

2. Adverse effects of Δ^9-THC

Cannabis sativa L. was and is the most used drug by human beings for hedonistic purposes (UNODC, 2003). And even so, until the recent past, it was not considered as a potent inducer, if at all, of dependence in humans, this being due to the way dependence was defined in the past (Swift and Hall, 2002). However, with the adoption of the DSM-III and other similar criteria to define dependence, there have been recent reports stating that a certain proportion of chronic marihuana users may become dependent (Anthony et al., 1994; Budney et al., 2001; Swift et al., 2001a, b). Another point deserving attention is the very low incidence of ill effects under chronic use. For example,

Russo et al. (2002) described four patients who participated in a Compassionate Investigational New Drug (IND) Program of the American FDA, smoking standardized, heat-sterilized quality-controlled low grade marihuana cigarettes, for 11–27 years. Aside from mild changes in pulmonary function observed in two patients, no other physiological and neurological disturbances were found.

When the subject comes to Δ^9-THC, the dependence issue becomes clearer. Due to the enormous progress in chemistry, pharmacology, toxicology and clinical pharmacology of Δ^9-THC, leading to its clini ' usefulness, the United Nations in 1991 changed the status of Δ^9-THC, by removing it from Schedule I (use only for research purposes) and placing it in Schedule II (medical use allowed under strict control of production, trade and stocks) of the 1971 Convention on Psychotropic Drugs. Abstinence symptoms, after being exposed to rather large doses of Δ^9-THC (80–210 mg/day) were observed in humans participating in clinical laboratory experiments (Jones et al., 1981; Haney et al., 1999). However, according to the WHO Expert Committee on Drug Dependence, abuse of Δ^9-THC is rare (WHO, 2003); thus, from 103 countries responding a WHO questionnaire, only two indicated some abuse of Δ^9-THC: Denmark and USA. Actually, the United States informed that only three cases of Δ^9-THC abuse during the 1992–1994 period were reported by the American Association of Poison Control Centers. In this context it is rather interesting that anandamide has little if any capacity to induce abstinence symptoms and physical dependence in rats (Aceto et al., 1998).

Based on these facts, the WHO Expert Committee on Drug Dependence further considered that the abuse liability of Δ^9-THC does not constitute a substantial risk to public health and proposed that Δ^9-THC should be rescheduled to schedule IV of the United Nations 1971 Convention on Psychotropic Substances (WHO, 2003).

Δ^9-THC does not cause prominent physical changes in users; some degree of dry mouth, blurred vision and ataxia may be reported, and objectively, an increase in heart rate occurs (Carlini et al., 1974).

Δ^9-THC may adversely affect the psyche, cognition and the psychomotor performance of humans. Examples of acute effects on cognitive functions are: impairment and even loss of the capacity to discriminate or to produce time and distance intervals (Karniol and Carlini, 1973; Carlini et al., 1974; for review see Grotenhermen, 2002b). Thus, volunteers receiving 5–20 mg of Δ^8 or Δ^9-THC delivered through inhalation perpetrated gross errors when producing a time interval of 60 s; this unwanted effect was present up to at least for 20 min after the cannabinoids aspiration (Karniol and Carlini, 1973). Other ill effects are a decrease of vigilance, of the ability to inhibit responses and to perform arithmetic tasks (for reviews see Leweke, 2002; Iversen, 2003).

Among the psychic effects of acute administration of Δ^9-THC are feelings of well being, relaxation and anxiolysis; users may also suffer unpleasant reactions, such as disconnected thoughts, panic reactions, feelings of depersonalization, disturbing changes in perception, delusions and hallucinatory experiences (for reviews see Campbell et al., 2001; Leweke, 2002).

The long-term effects of Δ^9-THC on the psyche, cognition and brain structures of human beings are not yet, known, as there are not reports of prolonged use of Δ^9-THC. Thus, there is no mention in the scientific literature of an 'motivational syndrome' caused by the cannabinoid; furthermore it is worth mentioning that even for chronic marihuana use there is no conclusive evidence for the occurrence of this syndrome (Hall and Solowij, 1997; Hollister, 1998; Solowij and Grenyer, 2002; Iversen, 2003).

Similarly, there are no data in scientific literature reporting neuropathological changes in the brain of Δ^9-THC users; actually, such changes have not been convincingly demonstrated in the brain of marihuana users (for review see Iversen, 2003).

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6.

THE HEALTH AND PSYCHOLOGICAL EFFECTS...

"The health and psychological effects of cannabis use"

Wayne Hall, et al.
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2001

The health and psychological effects of cannabis use

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The health and psychological effects of cannabis use

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Louisa Degenhardt
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Glossary

Term	Definition
Acute effects	The immediate, short-term effects of using a drug
AIDS	Acquired Immune Deficiency Syndrome
Allogenic lymphocytes	Cell types that induce distinct immune responses from an organism
AMA	Australian Medical Association
Amotivational syndrome	A pattern of behaviour characterised by a lack of motivation, energy and initiative
Analgesic	A drug which reduces pain
Anandamide	A natural cannabinoid found in the brain
Anorexia	Significant loss of weight, which can affect HIV patients
Antagonist	A substance that blocks the positive effects of a drug
Anti-emetic	A drug that reduces nausea and vomiting
ARGT	Australian Register of Therapeutic Goods
Asphyxiation	Choking, suffocation
BMA	British Medical Association
Burden of disease	The effect that a disorder has upon society measured by the years of life lost and amount of disability it causes
Cachexia	Significant loss of lean body mass such as skeletal muscle, which can affect cancer and HIV patients
Cannabinoids	Chemicals that act upon the same receptor sites in the brain as THC
Cannabis	All forms of the product of the *cannabis sativa* plant
Carcinogen	A substance that causes cancer
Cardiac arrhythmias	Irregular heart rhythms that can be fatal
Cardiomyopathy	General term for diseases of the heart muscle
CB1 and CB2	Two types of receptors found in the cannabinoid system
CBD	Cannabidiol, a cannabinoid without the psychoactive effects of THC
CD&SA	The Canadian Controlled Drug and Substances Act

Cerebrovascular disease	Atherosclerosis of the arteries in the brain that can lead to stroke: damage caused in the brain by blood clot or other obstruction interrupting the flow of blood and hence of oxygen to the brain
Chronic effects	The longer-term effects of drug use that may occur if drug use is continued over months or years
Cisplatin	Drug used to treat prostate bladder, ovary, head and neck cancers
Cohort	Any designated group of persons who have been exposed to some event (e.g. use of cannabis)
Cohort study	A study design in which people who have and have not been exposed (e.g. to cannabis) are followed up to see how many develop a disease
COPD	Chronic obstructive pulmonary disease
Coronary atherosclerosis	A disease in which deposits of cholesterol and fats form block the arteries that supply the heart muscle. It may lead to a 'heart attack'
Cross-over study design	Study in which participants received two or more treatments without their knowledge to see whether they respond differently to them
Cross-sectional study	A study design in which the health status and risk factors of a sample are assessed at one point in time e.g. a survey
DAWN	The US Drug Abuse Warning Network
DEA	The US Drug Enforcement Administration
Dependence (drug)	A disorder in which persons experience loss of control over drug use, and continue to use the drug despite the problems it causes them (see pp 75-76 for criteria)
DHHS	The US Department of Health and Human Services
Dopamine	A chemical that acts as a neurotransmitter in the brain
Double blind study	A study in which neither the patient nor the treating physician know whether the patient is receiving an active or placebo drug
Dronabinol	Synthetic THC, which is taken orally in a capsule with sesame oil
Dysphoria	Unhappy mood (as opposed to euphoria)
Emesis	Nausea and vomiting
Emetogenic	Causing vomiting and nausea

Endogenous cannabinoids	Cannabinoids that naturally occur in the brain, such as anandamide
Epidemiological research	Research that studies the occurrence of disease or risk factors for disease in the general population
Epilepsy	A disorder in which abnormal brain electrical activity causes seizures
Experimental study	A study design in which exposure to a key factor is under the researcher's control, e.g. when two groups of people are randomly assigned to receive a drug or a placebo
F&DA	The Canadian Food and Drugs Act
FAS	Foetal alcohol syndrome
FDA	The US Food and Drug Administration
Foetal alcohol syndrome (FAS)	Condition that results from a foetus being exposed to alcohol; it is marked by decreased alertness, hyperactivity, intellectual disability, motor problems, heart defects and facial abnormalities
Glaucoma	A disease caused by raised intra-ocular pressure that, if untreated, can cause blindness
Histopathological	Abnormality of the structure of bodily tissues
HIV	The Human Immunodeficiency Virus which causes AIDS
Humoral	Pertaining to the blood or the fluids of the body
Huntington's disease	A movement disorder caused by a dominant gene, producing pathological brain changes, including in areas controlling movement
Hypertension	High blood pressure
Hypomania	A condition in which people are energetic and have elevated mood
Illicit drugs	Drugs which adults are prohibited from using by law
Immunosuppressive	Anything (e.g. a drug, radiation, viral infection) that suppresses the functioning of the body's immune system
INCB	The United Nations' International Narcotics Control Board
IND	A program of the FDA that allows patients with serious or life-threatening diseases to use experimental drugs
IOM	Institute of Medicine, US

IOP	Intra-ocular pressure; pressure within the eyeball
Longitudinal study	A synonym for a cohort study
Lower brainstem	Areas of the brain including the cerebellum that control movement and respiration
Marijuana	Leaves and flowering tops of the *cannabis sativa* plant
Ma. inol	The trade name for dronabinol
Metabolites	Chemical products of a drug that are produced when it is processed in the body
Mitogens	Substances that induce cell transformations
MS	multiple sclerosis
mutagen	an agent or substance that induces genetic mutation in cells
Nabilone	A synthetic drug that has similar effects to THC
Narcotic	A legal term for drugs prohibited by international drug treaties that includes opioids, cocaine and cannabis
NCR	The Canadian Narcotic Control Regulations
NDA	An investigational New Drug Application, one step in the process in the US for approving drugs for medical use
Negative symptom	In schizophrenia, absence of a behaviour ordinarily seen in 'normal' people, such as initiative
NIDA	The US National Institute on Drug Abuse
n-of-1 clinical trial	Trial in which a single patient receives a drug and a placeb and their behaviour is measured under double blind conditions
NORML	The US National Organization for Reform of Marijuana Legislation
Odds ratio	A ratio of the odds of disease in persons who are and are not exposed to some factor. It measures the strength of the association between the factor and the disease
ONDCP	The US Office of National Drug Control Policy
Organic symptoms	Symptoms that are ascribed to physical (organic) causes
Pancreatitis	Acute or chronic inflammation of the pancreas
Parkinson's disease	A movement disorder that results from damage to area of the brain involved in movement control

Pharmacopeia	A book containing a list of products used in medicine, with descriptions, tests for purity and identity, and dosages
Placebo	An inactive drug that is indistinguishable in appearance from the active drug with which it is being compared
PLWHA	Association for People Living With HIV/AIDS
Positive symptoms	In schizophrenia, presence of a behaviour not seen in 'normal' people, such as hallucinations and delusions
Premorbid	A person's behaviour or personality prior to the onset of an illness
Prevalence	The number of cases of an illness or disease that are present in the total population in a specified period of time e.g. a year
Prodromal	In schizophrenia, symptoms that precede the onset of the illness
Prospective study	A synonym for a cohort study
Psychoactive drug	A drug that affects feeling, memory and thinking
Psychomotor	Having to do with voluntary movement
Psychostimulants	Drugs that have stimulating effects and increase psychomotor activity
Psychotomimetic drugs	Drugs that produce symptoms of psychosis, such as visual hallucinations, delusions and distorted perception
R&D	Research and development
RACP	Royal Australian College of Physicians
Randomised controlled trial	A clinical trial to evaluate a treatment in which participants are randomly assigned to receive an active drug or a placebo
RCT	Randomised controlled trial
Relative risk	A ratio of the rate of disease among persons exposed to a factor (e.g. cannabis use) and the rate among those who are not exposed
Resorption	To absorb again (from the Latin meaning 'to suck back')
Retrospective study	A study design in which exposure to a risk factor (e.g. drug use in adolescence) is determined retrospectively (e.g. by asking an adult about their drug use in early adolescence)
SAP	The Canadian Special Access Program

SCOST	House of Lords Select Committee on Science and Technology
Stress-diathesis model	A model of schizophrenia in the disorder is precipitated among vulnerable individuals (those with the diathesis) by life stressors
Temporal lobe	An area on either side of the brain that is involved in memory and emotion
Teratogen	A substance that produces abnormalities in a foetus during its development in the uterus
TGA	The Australian Therapeutic Goods Administration
THC	Delta-9-tetrahydrocannabinol, the principal psychoactive ingredient of cannabis
Titrate	To measure the dose of a drug against its effects
Tourette's syndrome	A movement disorder that results from damage to area of the brain involved in movement control
Toxic psychotic disorder	A psychosis caused by high doses of a drug or other substance
TPP	The Canadian Therapeutic Products Programme
Viscous	A substance that is sticky or glutinous

Executive summary

This review of the health and psychological effects of cannabis updates an earlier review (commissioned by the National Task Force on Cannabis in 1992) in the light of recent research and reviews by the World Health Organization (1997) and the US Institute of Medicine (1999).

Assessing the health effects of cannabis

There are a number of reasons why it is difficult to evaluate the health risks of using cannabis or any drug. First, it is difficult to decide whether use of a drug causes an adverse effect on human health when there is a long interval between its use and the appearance of the adverse effect. It takes time for such adverse effects to develop and for research to identify them.

Second, there is a trade off between the rigour and relevance of different types of evidence when making causal inferences. The most rigorous evidence is provided by laboratory investigations using animals or cell preparations in a test tube in which known drug doses can be related to measured biological outcomes. The relevance of this evidence to human disease is uncertain. Epidemiological studies of relationships between drug use and human disease are of greater relevance but the increased relevance is obtained at the cost of reduced rigour. Doses of illicit drugs used over periods of years are difficult to quantify because of the varied dosages of blackmarket drugs and stigma in admitting to illicit drug use. Interpretation is complicated by the fact that regular cannabis users often also use alcohol, tobacco and other illicit drugs.

The criteria for causal inference that we use are the standard ones: (1) evidence that there is a relationship between cannabis use and a health outcome provided by one of the accepted types of research design (namely, case-control, cross-sectional, cohort, or experiment); (2) evidence provided by a statistical test or confidence interval that the relationship is unlikely to be due to chance; (3) good evidence that drug use precedes the adverse effect (e.g. from a cohort study); and (4) evidence either from experiment, or observational studies with statistical or other form of control, that it is unlikely that the relationship is due to some other variable which is related to both cannabis use and the adverse health effect.

In the trade-off between relevance and rigour, we give more weight to human clinical and epidemiological evidence. In the absence of human evidence, animal experiments raise a suspicion that cannabis use has an adverse effect on human health. The degree of suspicion is in proportion to: the number of studies; the consistency of results across different species; and the degree of expert consensus on the extent to which findings in animals predict adverse effects in humans considering current patterns of cannabis use.

Cannabis the drug

Cannabis is the name for preparations from the plant *Cannabis sativa*. Laboratory research on animals and humans has demonstrated that the primary psychoactive constituent in cannabis is delta-9-tetrahydrocannabinol, abbreviated as THC. THC is found in a sticky resin that covers the flowering tops and upper leaves in the female plant.

The cannabinoid receptor

Cannabis acts upon specific receptors or molecules in the brain and immune system. These receptors are found in areas of the brain that underlie the psychoactive and other effects of cannabis use. Two 'endogenous' or naturally occurring molecules have been discovered in the brain and body which bind to the cannabinoid receptor and mimic the action of THC. These discoveries promise to improve our understanding of the role played by the cannabinoid system in the brain and explain the mechanism of action of cannabis.

Forms of cannabis

The concentration of THC varies between the three forms of cannabis: marijuana, hashish and hash oil. Marijuana is prepared from the dried flowering tops and leaves of the plant. Its potency depends upon the growing conditions, the genetic characteristics of the plant and the proportions of leaves and 'heads'. The flowering tops have the highest THC concentration, with potency decreasing through the upper leaves, lower leaves, stems and seeds. The concentration of THC in marijuana containing mostly leaves and stems may range from 0.5 to 5%, while heads of the 'sinsemilla' variety may have THC concentrations of 7 to 14%. The THC content of cannabis seized in the USA in the past two decades has increased although not to the extent sometimes claimed in the media.

Hashish or hash consists of dried cannabis resin and compressed flowers. The concentration of THC in hashish generally ranges from 2% to 8%. Hash oil is a highly potent and viscous substance obtained by extracting THC from hashish (or marijuana) with an organic solvent. The concentration of the THC in hash oil is generally between 15 and 50%.

Routes of administration

Cannabis is often smoked in a hand-rolled 'joint', like a cigarette. Tobacco is often added to assist burning. Hashish may also be mixed with tobacco and smoked as a joint, but it is probably more frequently smoked in a pipe. A water pipe known as a 'bong' is a popular way of smoking all cannabis preparations because the water cools the hot smoke before it is inhaled and less of the drug is lost through sidestream smoke. A few drops of hash oil may be applied to a cigarette or a joint, to the mixture in the pipe, or the oil may be heated and the vapours inhaled. Cannabis smokers often inhale deeply and hold their breath for several seconds to ensure maximum absorption of THC by the lungs.

Hashish may also be eaten in cooked or baked foods. When swallowed the onset of the psychoactive effects of THC is delayed by about an hour and the 'high' is of lesser intensity although it may last several hours longer. It is easier to achieve the desired level of intoxication by smoking than swallowing cannabis since the effects are more immediate. THC is insoluble in water, so it is rarely injected.

Dosage

A typical joint contains between 0.5 and 1.0 g of cannabis plant matter and between 5 and 150 mg of THC. Between 20% and 70% of the THC is found in the smoke that reaches the lungs; the rest is burnt and lost in sidestream smoke. Only 5% to 24% of THC in the joint reaches the bloodstream when cannabis is smoked.

Only a small amount of cannabis (delivering 2 to 3 mg of THC) will produce a brief high in an occasional user, and a single joint may be enough for two or three such individuals. A heavy cannabis smoker may use five or more joints per day, while heavy users in Jamaica, for example, may consume up to 420 mg THC per day.

Metabolism of cannabinoids

Different methods of using cannabis lead to differing absorption, metabolism and excretion of THC. When smoked, THC is absorbed from the lungs into the bloodstream within minutes. It is first metabolised in the lungs, and then in the liver where it is transformed to a number of metabolites. The first of these, 9-carboxy-THC, is detected in blood within minutes of smoking. When swallowed, THC takes 1 to 3 hours to enter the bloodstream, delaying the onset of psychoactive effects. Another major metabolite, 11-hydroxy-THC, which is 20% more potent than THC and penetrates the brain more rapidly than THC, is found in high concentrations after being swallowed.

THC and its metabolites account for most of the subjective effects of cannabis. Peak blood levels of THC are usually reached within 10 minutes of smoking, and decline to about 5-10% of their initial level within an hour. This rapid decline reflects the rapid conversion of THC to its metabolites and the distribution of THC to fatty tissues, including the brain.

THC and its metabolites are highly fat soluble, so they may remain in the fatty tissues of the body for long periods of time. THC and its metabolites accumulate in the body because of their slow rate of clearance They may be detected in the blood for several days and traces may persist for several weeks. THC may be stored in body fat for more than 28 days.

Detection of cannabinoids in body fluids

Cannabinoid levels in the blood vary between individuals and depend on the dose received and the individual's history of cannabis use. Blood levels of THC may range between 0 to 500 ng/ml, depending on the potency of the cannabis and the time since smoking. The detection of THC in blood above 10 to 15 ng/ml is evidence of recent use, although it is difficult to be precise about how recent. A more precise estimate of time since last use is provided by the ratio of THC to 9-carboxy-THC. Similar blood concentrations of THC and this metabolite indicate that cannabis has been used in the past 20-40 minutes and so suggest a high probability of intoxication, although this is less clear in regular users.

Cannabis intoxication impairs skills required to drive a motor vehicle, so it would be desirable to have a measure of cannabis intoxication similar to the breath test for alcohol intoxication. The major obstacle is the lack of a simple relationship between blood levels of THC (and its metabolites) and degree of psychomotor impairment.

Storage of THC

With repeated frequent dosing of cannabis THC accumulates in fatty tissues in the human body where it may remain for considerable periods of time. The health significance of this storage is unclear. The storage of cannabinoids *would* be serious cause for concern if THC were a highly toxic substance that remained physiologically active while stored in body fat. THC is not a highly toxic substance and it is inactive while stored in fat. Stored cannabinoids could conceivably be released into blood producing a 'flashback', although this is likely to occur very rarely, if at all.

Increasing potency of cannabis?

It has been claimed that the medical literature underestimates the adverse health effects of cannabis because it is based on research conducted on less potent forms of cannabis than have become available in the past decade. The evidence suggests that the average potency of cannabis has increased but not to the extent often claimed. Changes in patterns of cannabis use, with earlier age of first use and more regular use of more potent forms of cannabis, have probably been more important in increasing average dose of THC than any increase in the THC content of cannabis plants.

Patterns of cannabis use

In Australia in 1998, 40% of adults reported that they had used cannabis at some time in their lives. Cannabis is usually smoked in Australia in a water pipe or joint. Survey data from European countries generally shows lower rates of use than in Australia, Canada and the USA. The highest rates of use in Europe are in the United Kingdom, Denmark and France.

In Australia most young people have tried cannabis at some time in their lives. Regular cannabis use is much less common, with most cannabis users using intermittently and discontinuing their use. Males are more likely than females to have ever used cannabis and to have used in the past year or past month. Rates of use are highest in young adults in their early 20s. The natural history of cannabis use, documented in longitudinal studies conducted in the USA, is for use to begin in the mid to late teens, to reach a maximum in the early 20s and to decline in the mid to late 20s. A minority of cannabis users continue to use the drug into their 30s. Cannabis use substantially decreases after marriage and parenthood.

Only a small proportion of cannabis users use the drug for several years or more. The daily or near daily use pattern over a period of years is the pattern with the greatest risk of experiencing adverse health and psychological consequences. Daily cannabis users are more likely to be male and less well educated; they are also more likely to regularly use alcohol and to have experimented with a variety of other illicit drugs including amphetamine and other psychostimulants, hallucinogens, sedatives and opioids.

Acute psychological and health effects

The main reason people use cannabis is to get 'high' that is, to experience euphoria, relaxation, and perceptual alterations, and the intensification of ordinary sensory experiences, such as eating, watching films, and listening to music. The 'high' may be accompanied by infectious laughter and talkativeness. Cognitive effects include impaired short-term memory and a loosening of associations. Motor skills and reaction time are also impaired.

The most common unpleasant effects of cannabis are anxiety, panic reactions, and depressive feelings. These are most common among users who are unfamiliar with the drug's effects, and by patients who have been given THC for therapeutic purposes. Experienced users may occasionally report these effects after swallowing cannabis, as the desired dose is harder to estimate, with the result that the effects may be more pronounced and last longer than those experienced after smoking cannabis. These effects can be managed by reassurance and support. Psychotic symptoms such as delusions and hallucinations may be experienced but only rarely and following very high doses.

A few minutes to a quarter of an hour after cannabis is smoked or swallowed, THC increases heart rate by 20% to 50%. This may last for up to three hours. Blood pressure is increased while the person is sitting and decreases on standing. In healthy young users these cardiovascular effects are unlikely to be of any clinical significance because tolerance develops to the effects of THC, and young, healthy hearts will only be mildly stressed. These effects may pose more of a risk to patients with heart disease.

The acute toxicity of cannabis, and cannabinoids generally, is very low. There are no cases of fatal cannabis poisoning in the human medical literature. Animal studies indicate that the dose of THC required to produce 50% mortality in rodents is extremely high by comparison with other pharmaceutical and recreational drugs. The lethal dose also increases as one moves up the phylogenetic tree, suggesting that the lethal dose in humans could not be achieved by smoking or swallowing cannabis.

Psychomotor effects and driving

Cannabis intoxication impairs a wide range of cognitive and behavioural functions that are involved in driving an automobile or operating machinery. The effects are generally larger, more consistent and more persistent in tasks that require sustained attention. Recreational doses of THC produce similar performance impairments in laboratory tests and standardised driving courses to Blood Alcohol Concentrations of between 0.07% and 0.10%.

It is difficult to estimate how these impairments affect the risk of being involved in motor vehicle accidents. Studies of the effect of cannabis on driving performance on the road have found only modest impairments because cannabis intoxicated drivers drive more slowly, and take fewer risks, than alcohol intoxicated drinkers. Cannabis users seem to be more aware of their psychomotor impairment than alcohol users.

There is currently no controlled epidemiological evidence that cannabis users are more likely than non-users to be involved in motor vehicle or other accidents. This contrasts

with alcohol use where case-control studies show that persons intoxicated by alcohol are over-represented among accident victims.

Cannabinoids are found in between 4% and 37% of blood samples of motor vehicle accident victims but these findings are difficult to evaluate for the following reasons. First, we do not know whether persons with cannabinoids are over-represented among accident victims because we do not know how often cannabinoids are found in the blood of persons who are *not* involved in accidents. Second, cannabinoids in blood indicate recent use but they do not necessarily mean that the driver was intoxicated at the time of the accident. Third, 75% of drivers with cannabinoids in their blood also have high blood alcohol levels, making it difficult to separate the effects of cannabis on accident risk from those of alcohol.

Household survey data suggest that cannabis users are 2 to 4 times more likely to be represented among accident victims than non-cannabis users. Cannabis users who also use alcohol are even more highly over-represented among the victims of motor vehicle accidents. The separate effects of alcohol and cannabis on psychomotor impairment and driving performance are approximately additive.

The effects of chronic cannabis use

Cellular effects and cancers

There is weak evidence that THC can alter cell metabolism and DNA synthesis in the test tube. There is stronger evidence that cannabis *smoke* produces mutations in cells in the test tube and in live animals, and hence is a potential cause of cancer. Cannabis smoke contains many of the same carcinogenic substances as cigarette smoke. If cannabis smoking causes cancer it is most likely to be cancers of the lung and upper aerodigestive tract that are maximally exposed to cannabis smoke.

Aerodigestive tract cancers have been reported among young adults who have been daily cannabis users and a case-control study has found an association between cannabis smoking and head and neck cancer. A prospective cohort study of 64,000 adults did not find an increased incidence of head and neck or respiratory cancers but it found increased rates of prostate cancer. The relative youth of the participants, and their low rates of regular cannabis use, may have reduced the ability of this research to detect an increase in respiratory cancers. Further studies are needed to clarify the issue.

There is much weaker evidence for an increased risk of cancers among children born to women who smoked cannabis during pregnancy. Three studies of very different types of cancer have reported an association with maternal cannabis use. None of these was a planned study of the role of cannabis use in these cancers so a replication of their results is required. There have not been any increases in the rates of these cancers that parallel increased rates of cannabis use over the past three decades.

Immunological effects

Cannabinoids impair cell-mediated and humoral immunity in rodents and reduce resistance to infection by bacteria and viruses in animals. Cannabinoid receptors are

expressed in cells of the immune system in animals and humans although the significance of this for immune function is unclear. Cannabis smoke also impairs the functioning of alveolar macrophages, the first line of the body's immune defence system in the lungs. The clinical relevance of these findings is uncertain because the doses required to produce these effects have been very high, and extrapolation to the doses used by humans is complicated by the fact that tolerance may develop to these effects.

The limited experimental and clinical evidence in humans suggests that the adverse effects seen in animals are not replicated in humans. There is no conclusive evidence that cannabinoids impair immune system function in humans, as measured by T-lymphocytes, B-lymphocytes or macrophages, or immunoglobulin levels. There is suggestive evidence that THC impairs T-lymphocyte responses to mitogens and allogenic lymphocytes.

The clinical and biological significance of these possible effects in chronic cannabis users is uncertain. There is no epidemiological evidence of increased rates of disease among chronic heavy cannabis users, and several large prospective studies of HIV-positive homosexual men have found that cannabis use does **not** increase the risk of progression to AIDS.

Reproductive effects

Chronic administration of THC disrupts male and female reproductive systems in animals, reducing testosterone secretion, and sperm production, motility, and viability in males, and disrupting the ovulatory cycle in females. It is uncertain whether cannabis use has these effects in humans because of the inconsistency in the limited literature on human males, and the lack of research in the case of human females. There is uncertainty about the clinical significance of these effects in normal healthy young adults.

It is likely that cannabis use during pregnancy impairs foetal development, leading to smaller birthweight, perhaps as a consequence of shorter gestation, and probably by the same mechanism as cigarette smoking. There is no clear evidence that cannabis use during pregnancy increases the risk of birth defects as a result of exposure of the foetus to cannabis in the uterus.

There is some evidence that infants exposed to cannabis in the uterus may show transient behavioural and developmental effects during the first few months after birth. These effects are small by comparison with those caused by tobacco use during pregnancy, and have not been observed in all studies.

The cardiovascular system

The changes that cannabis causes in heart rate and blood pressure are unlikely to harm healthy young adults, but they may be less benign in patients with hypertension, cerebrovascular disease and coronary atherosclerosis, in whom cannabis smoking may pose a threat because it increases the work of the heart. The seriousness of these effects will be determined as the cohort of chronic cannabis users of the late 1960s enters the age of maximum risk for atherosclerosis in the heart, brain and peripheral blood vessels. These effects could be life threatening in patients with heart disease.

The respiratory system

Regular cannabis smoking impairs the functioning of the large airways and causes symptoms of chronic bronchitis such as coughing, sputum, and wheezing. Given that tobacco and cannabis smoke contain similar carcinogenic substances, and that tobacco smoke has adverse effects on the respiratory system, it is likely that chronic cannabis use also increases the risks of respiratory cancer. There is evidence that chronic cannabis smoking produces histopathological changes in lung tissues of the type that precede the development of lung cancer. Concern about the possibility of cancers caused by chronic cannabis smoking has been raised by case reports of cancers of the aerodigestive tract in young adults with a history of heavy cannabis use. A recent case-control study has provided the first evidence of an increased risk of aerodigestive tract cancers among cannabis smokers.

Gastrointestinal system

There is no human or animal evidence that cannabinoids adversely affect liver function. Animal studies show that cannabinoids affect intestinal motility and delay gastric emptying but this is of little significance. The most interesting gastrointestinal effect of cannabis is its potential therapeutic use to reduce nausea and stimulate appetite in cancer and AIDS patients.

Psychological effects of chronic cannabis use

Motivational effects

The evidence that chronic heavy cannabis use produces an amotivational syndrome consists largely of case studies. Controlled field and laboratory studies have not found evidence for such a syndrome, although their value is limited by the small sample sizes and limited sociodemographic characteristics of participants of the field studies, the short periods of drug use, and the youth, good health and minimal demands made of the volunteers in the laboratory studies. If there is such a syndrome, it is a relatively rare occurrence, even among heavy, chronic cannabis users. The phenomenon may be better explained as the result of chronic intoxication in dependent cannabis users.

A dependence syndrome

There is good evidence that a cannabis dependence syndrome (as defined in DSM-IV) can occur in heavy chronic users of cannabis. Regular cannabis use produces tolerance to the effects of THC and some users report withdrawal symptoms on cessation of use. There is clinical and epidemiological evidence that *some* heavy cannabis users experience problems controlling their cannabis use, and continue to use despite adverse personal consequences of use.

Surveys in the USA and Australia show that cannabis dependence is the most common form of drug dependence after alcohol and tobacco. The risk of developing dependence is about: one in ten among those who ever use the drug; between one in five and one in three among those who use cannabis more than a few times; and around one in two among those who become daily users. The prevalence of drug-related problems may be low by comparison with those of alcohol dependence and there is likely to be a high rate of remission of cannabis dependence without formal treatment. Treatment should

probably be based on the same principles as treatment for other forms of dependence, although this issue is also in need of research.

Cognitive effects

The weight of evidence suggests that long term heavy use of cannabis does not produce severe impairment of cognitive function like that observed in heavy alcohol users. There is evidence that it may produce more subtle cognitive impairment in the higher cognitive functions of memory, attention and organisation and integration of complex information. This evidence suggests that the longer cannabis is used, the more pronounced will be the cognitive impairment. It remains to be seen whether the impairment can be reversed after an extended period of abstinence.

Psychotic disorders

There is suggestive evidence that heavy cannabis use can produce an acute toxic psychosis during intoxication with symptoms of confusion, amnesia, delusions, hallucinations, anxiety, agitation and hypomania. The evidence comes from laboratory studies of the effects of THC on normal volunteers and clinical observations of psychotic symptoms in heavy cannabis users which seem to resemble those of other toxic psychoses and which remit rapidly following abstinence.

There is less support for the hypothesis that cannabis use can cause a psychosis which persists beyond the period of intoxication. There is suggestive evidence that chronic cannabis use may precipitate a psychosis in vulnerable individuals. This is only suggestive because in the best study conducted to date, the use of cannabis was not documented at the time of diagnosis, cannabis use may have been confounded by amphetamine use, and there were doubts about whether the study could distinguish between schizophrenia and acute drug-induced psychoses. The relationship is unlikely to be causal, because the incidence of schizophrenia has either remained stable, and possibly declined, while cannabis use has increased among young adults.

Effects on adolescent development

Cross-sectional and longitudinal studies of adolescents in the 1970s and 1980s indicate that chronic heavy cannabis use may adversely affect adolescent development in a number of ways. Interpretation of this evidence is complicated by the fact that many of the indicators of adverse development which have been attributed to cannabis use precede its use, and make it more likely that a young person will use cannabis. These include minor delinquency, poor educational performance, nonconformity, and poor adjustment.

The gateway hypothesis

Among American adolescents in the 1970s and 1980s the typical sequence of initiation into drug use was that the use of alcohol and tobacco preceded the use of cannabis, which in turn, preceded the use of hallucinogens, amphetamine, and the later use of heroin and cocaine. Generally, the earlier the age of first use, and the greater the involvement with any drug in the sequence, the more likely a young person was to use the next drug in the sequence.

The explanation of cannabis' role in this sequence remains controversial. The evidence for the hypothesis that cannabis use has a pharmacological effect that increases the risk of using later drugs in the sequence is not strong. More plausible hypotheses are that it reflects a combination of: th early recruitment into cannabis use of nonconforming and deviant adolescents who are likely to use alcohol, tobacco and illicit drugs; a genetic vulnerability to become dependent on a range of substances; and socialisation of cannabis users within an illicit drug using subculture which increases the exposure, opportunity, and encouragement to use other illicit drugs.

Adolescent psychosocial outcomes

In cross-sectional surveys of young people, cannabis use is related to failing to complete a high school education and job instability in young adulthood. The complication is that those who are most likely to use cannabis have lower academic aspirations and poorer school performance *before* using cannabis than those who do not. When these differences are taken into account, the relationship between cannabis use and educational and occupational performance is much more modest. Even so, the adverse effects of cannabis and other drug use upon educational performance are important because they further impair poor performance, and level of education affects choice of occupation, level of income, choice of mate, and quality of life.

There is also suggestive evidence that heavy cannabis use has adverse effects upon family formation, mental health, and involvement in drug-related (but not other types of) crime. In the case of each of these outcomes the apparently strong associations revealed in cross-sectional data are much more modest in longitudinal studies which statistically control for associations between cannabis use and other variables which predict these adverse outcomes.

Therapeutic Effects of Cannabinoids

There is reasonable evidence that THC is an effective anti-emetic agent for patients undergoing cancer chemotherapy. It was as effective as the drugs widely used in the late 1970s and early 1980s when most of the research was conducted but THC does not appear to be as effective as newer anti-emetic drugs.

There is reasonable evidence that THC and cannabis are effective in treating AIDS-related wasting. There is suggestive evidence that cannabinoids are useful as anti-spasmodic, and anti-convulsant agents that warrants further clinical research. There are other potential therapeutic uses which require more pharmacological and experimental investigation, such as, the use of cannabinoids as analgesics or antispasmodics in disorders such as multiple sclerosis.

THC and other cannabinoids have not been widely used therapeutically or investigated in clinical trials. This is because in the United States where most cannabis research has been conducted, clinical research on cannabinoids has been discouraged by regulation and the fact that THC, the most therapeutically effective cannabinoid, is the one that produces the psychoactive effects sought by recreational users. THC is also a naturally occurring substance that cannot be patented, which means that companies are unlikely to

conduct research into its medical uses. The discovery of a cannabinoid receptor and the cannabinoid-like substance anandamide may encourage more basic research into the therapeutic uses of natural and synthetic cannabinoids.

Overall evaluation of the health and psychological risks of cannabis use

Acute effects

The major acute adverse psychological and health effects of cannabis intoxication are:

- anxiety, dysphoria, panic and paranoia, especially in naive users;
- cognitive impairment, especially of attention and memory;
- psychomotor impairment, and possibly an increased risk of accident if an intoxicated person attempts to drive a motor vehicle;
- an increased risk of experiencing psychotic symptoms among those who are vulnerable because of personal or family history of psychosis; and
- an increased risk of low birth weight babies if cannabis is used during pregnancy.

Chronic effects

The most probable health and psychological effects of chronic heavy cannabis use appear to be:

- respiratory diseases associated with smoking as the method of administration, such as chronic bronchitis, and the occurrence of histopathological changes that may be precursors to the development of malignancy;
- an increased risk of cancers of the aerodigestive tract, i.e. oral cavity, pharynx, and oesophagus; and
- development of a cannabis dependence syndrome, characterised by an inability to abstain from or to control cannabis use.

The following **possible** adverse effects of chronic, heavy cannabis use remain to be confirmed by further research:

- a decline in occupational performance marked by underachievement in adults in occupations requiring high level cognitive skills, and impaired educational attainment in adolescents; and
- subtle forms of cognitive impairment, most particularly of attention and memory, which persist while the user remains chronically intoxicated, and may or may not be reversed by prolonged abstinence from cannabis.

High risk groups

A number of groups can be identified as being at increased risk of experiencing some of these adverse effects.

Adolescents

- Adolescents with a history of poor school performance whose educational achievement may be reduced by chronic intoxication with cannabis; and
- Adolescents who initiate cannabis use in the early teens who are at higher risk of progressing to regular cannabis use, to developing dependence on cannabis, and to using other illicit drugs.

Women of childbearing age

- The babies of women who continue to smoke cannabis during pregnancy may have lower birth weight.

Persons with pre-existing conditions

Persons with a number of pre-existing diseases who smoke cannabis are probably at an increased risk of exacerbating symptoms of their diseases. These include:

- Individuals with cardiovascular diseases, such as coronary artery disease, cerebrovascular disease and hypertension;
- Individuals with respiratory diseases, such as asthma, bronchitis, and emphysema;
- Individuals with schizophrenia; and
- Individuals who are dependent on alcohol and other drugs who are probably at an increased risk of developing dependence on cannabis.

Comparing the health risks of alcohol, tobacco and cannabis use

Comparing the adverse health effects of cannabis with those of alcohol and tobacco, reminds us of the health risks of two widely used psychoactive drugs. Cannabis shares a route of administration with tobacco smoking, and its effects resemble those of alcohol, which is also used for its intoxicating and euphoric effects.

Acute effects

Alcohol: The major risks of acute cannabis use are similar to the acute risks of alcohol intoxication in a number of ways. First, both drugs produce psychomotor and cognitive impairment. The impairment produced by alcohol increases risks of various kinds of accidents, and the likelihood of engaging in risky behaviour, such as dangerous driving and unsafe sexual practices. It remains to be determined whether cannabis intoxication produces similar increases in accidental injury and death.

Second, there is good evidence that substantial doses of alcohol taken during the first trimester of pregnancy can produce a foetal alcohol syndrome. There is weak but inconclusive evidence that cannabis used during pregnancy may have similar adverse effects.

Third, there is a major health risk of acute alcohol use that is *not* shared with cannabis. In large doses alcohol can cause death by asphyxiation, alcohol poisoning, cardiomyopathy and cardiac infarct. There are no recorded cases of overdose fatalities attributable to cannabis.

Tobacco: The major acute health risks that cannabis share with tobacco are the irritant effects of smoke upon the respiratory system, the adverse effects of carbon monoxide and other components of smoke on the cardiovascular system and the stimulating effects of both THC and nicotine on the cardiovascular system, which can be detrimental to persons with cardiovascular disease.

Chronic effects

Alcohol: A number of the risks of chronic alcohol use may be shared by chronic cannabis use. First, heavy users of both drugs may develop a dependence syndrome in which they experience difficulty in stopping or controlling their use. There is strong evidence of such a syndrome in the case of alcohol and reasonable evidence in the case of cannabis. A major difference between the two is that it is uncertain whether a withdrawal syndrome reliably occurs after dependent cannabis users abruptly stop their cannabis use whereas the abrupt cessation of alcohol use in severely dependent drinkers produces a well-defined withdrawal syndrome which can in rare cases be fatal if untreated.

Second, there is reasonable clinical evidence that the chronic heavy use of alcohol can produce psychotic symptoms and exacerbate psychoses in some individuals. There is suggestive evidence that chronic heavy cannabis use may produce a toxic psychosis and precipitate psychotic illnesses in predisposed individuals. There is better evidence that it can exacerbate psychotic symptoms in individuals with schizophrenia.

Third, there is good evidence that chronic heavy alcohol use can indirectly cause brain injury—the Wernicke-Korsakov syndrome—with symptoms of severe memory defect and an impaired ability to plan and organise. With continued heavy drinking, and in the absence of vitamin supplementation, the drinker may develop severe irreversible cognitive impairment. Chronic cannabis use does not produce cognitive impairment of comparable severity. It may produce more subtle deficits in cognitive functioning that may or may not be reversible after abstinence.

Fourth, there is reasonable evidence that chronic heavy alcohol use impairs occupational performance in adults and educational achievements in adolescents. There is suggestive evidence that chronic heavy cannabis use produces similar, albeit more subtle impairments in occupational and educational performance of adults and adolescents.

Fifth, there is good evidence that chronic, heavy alcohol use increases the risk of premature mortality from accidents, suicide and violence. There is no comparable evidence for chronic cannabis use, although dependent cannabis users who frequently drive while intoxicated with cannabis possibly increase their risk of accidental injury or death.

Sixth, alcohol use has been accepted as a contributory cause of cancer of the mouth, tongue and throat in men and women. There is some evidence that chronic cannabis smoking may also be a contributory cause of cancers of the mouth, tongue, throat, oesophagus, and lungs.

Tobacco: The major adverse health effects shared by chronic cannabis and tobacco smokers are chronic respiratory diseases, such as chronic bronchitis, and probably, cancers of the aerodigestive tract. The increased risk of cancer in the respiratory tract is a consequence of the shared route of administration by smoking. Chronic cannabis smoking may also share the cardiotoxic properties of tobacco smoking, although this possibility remains to be investigated.

Public health impact

Studies of deaths, disease, economic costs and disease burden attributable to alcohol, tobacco and illicit drugs differ in the way that they rank the impact of alcohol, depending upon whether they include the mortality benefit of moderate alcohol use or not. They all agree, however, that *on current patterns of use,* alcohol and tobacco are much more damaging to public health in developed societies than cannabis, which makes no known contribution to deaths and a minor contribution to morbidity.

These estimates cannot be used to predict what would happen if there was a major change in the prevalence of cannabis use, as may happen if cannabis were to become as freely available and as heavily promoted as alcohol and tobacco. All that can be said with confidence is that if the rate of cannabis use increased to the levels of cigarette smoking and alcohol use, its adverse impact on public health would increase. It is impossible to say precisely by how much.

1 Introduction

This monograph updates a review of the health and psychological effects of cannabis that was undertaken in 1993 at the request of a National Task Force on Cannabis. The Task Force commissioned this review because there had not been an international review of the health and psychological effects of cannabis since one was published in 1983 by the Addiction Research Foundation and World Health Organization (1). Since our review was published (2) the World Health Organization (3) and the US Institute of Medicine (4) have published reviews of the research that has been undertaken on the health effects of cannabis use. This review updates the earlier review in the light of recent research and authoritative reviews with the aim of providing as accurate and objective an analysis of the health risks of cannabis as the evidence allows. It also makes clear which issues remain uncertain.

1.1 Making causal inferences

We have used standard criteria in making causal inferences (5) about the health effects of cannabis. These require that the following conditions are met: that there is an association between cannabis use and an adverse health outcome; that chance is an unlikely explanation of the association; that cannabis use preceded the health outcome; and that plausible alternative causal explanations of the association can be excluded.

Evidence of an association between cannabis use and a health outcome is provided by a relationship between cannabis use and the health outcome observed in a case-control, cross-sectional, cohort, or experimental study. These study designs differ in the ease and expense with which they can be conducted and in the strength of the inference that they warrant about the association between cannabis use and the health outcome under study.

Evidence is required that chance is an unlikely explanation of any relationship observed between cannabis use and a health outcome. 'Unlikely to arise by chance ' is conventionally taken to mean that it is an event that would occur less than once in twenty trials (5% of the time). In the biomedical sciences, statistical tests and confidence intervals are used to evaluate the plausibility of this hypothesis.

If cannabis use is a cause of an adverse health effect then cannabis use should precede the health effect. Cross-sectional and case-control studies which assess cannabis use and health status at the same time often do not enable us to decide which came first, the cannabis use or the health outcome. This is a problem when age at which a health outcome first appears (e.g. school failure, schizophrenia) is around the age at which cannabis use begins, namely, late adolescence and early adulthood. The strongest evidence that cannabis use precedes the health effects would be provided by a cohort study or an experiment. In the former the researcher observes that cannabis use precedes the health effect while in the latter the experimenter would ensure by design that it did so.

The alternative explanation of an association between cannabis use and a health outcome that is the most difficult to exclude is that the association reflects an unmeasured variable that is the cause of both cannabis use and the health outcome. In cross-sectional surveys of high school-aged adolescents, for example, cannabis users perform more poorly at school than non-cannabis users (6). An 'obvious' explanation of this association is that cannabis use is a cause of poor school performance. An equally plausible hypothesis is that low intellectual ability or learning difficulties are causes of both poor school performance and cannabis use (7, 8).

Experiments in which persons were randomly assigned to use cannabis or not would provide the best way of ruling out such 'common causes'. Random assignment would ensure that adolescent cannabis users did not differ prior to using cannabis use from adolescents who did not. Hence, any later differences in educational performance could be attributed to cannabis use rather than to pre-existing differences in ability. For obvious reasons this option is not available. It is impossible for ethical and practical reasons to randomly assign individuals to cannabis use except when studying acute and innocuous health effects of use. It would be unethical to force some adolescents to use cannabis, and impractical, even if ethical, to prevent those who were assigned not to use cannabis from doing so.

Experiments using laboratory animals are the next best option to human experiments on some of the health effects of chronic cannabis use. In such studies, mice, rats, or monkeys are randomly assigned to receive either high doses of cannabis or placebo for substantial parts of their lives. The rates of various health outcomes (e.g. cancers, immunological changes, reproductive effects) are then compared between the experimental and control animals. This strategy has limited application in studying the psychological effects of chronic cannabis use because there are no animal models for mental illness, poor school performance, and personal adjustment. Even when animal models are available there are problems in extrapolating results across species which are compounded by the fact that humans and animals use different routes of administration (e.g. oral and injected in animals versus smoked in humans), different forms of cannabis (pure THC in many animal studies versus smoked cannabis plant in human use), and very different doses of THC (high doses in animals vs. long-term, low dosing of crude THC in cannabis products that are smoked by humans).

When a suitable animal model does not exist, and when randomisation of human subjects is impractical or unethical, epidemiological methods are used to rule out common causes in human studies. These use statistical methods to estimate the effect that cannabis use has on a health outcome, after adjusting for the effects of any differences between cannabis users and non-users that may affect the outcome (e.g. personal characteristics and life experiences before using cannabis). If the relationship persists after statistical adjustment, then confidence is increased that it is not attributable to the variables for which statistical adjustment has been made. This approach has been used, for example, in longitudinal studies of the effects of adolescent cannabis use on psychosocial outcomes (7–9).

1.2 An overall evaluation of causal hypotheses

A single research study, no matter how well done, does not permit us to decide whether cannabis use is a cause of an adverse health outcome. Causal hypotheses are evaluated in the light of a body of research using criteria of the sort outlined by Hill (10). These criteria are not sufficient for establishing that an association indicates a causal relationship since it is possible to be mistaken about a causal inference when the criteria have been met. But generally, the more of the criteria that are met, the more likely the association is to be causal.

Strength of association: the stronger a relationship is the better our ability to predict that cannabis use and a health effect co-occur. Stronger relationships are generally more deserving of trust than weaker ones that the relationship is less easily explained as artefacts of measurement or sampling.

Consistency: relationships which are consistently observed by different investigators, in different populations, using varied measures and research designs, are more credible than relationships which are not. The persistence of a relationship despite differences in sampling and research methods makes it unlikely that it can be explained by these factors.

Specificity exists when cannabis use is strongly associated with the outcome, and the health outcome is rare in non-cannabis users. This is a desirable but not a necessary condition. If there is specificity we can be more confident that there is a causal relationship but its absence does not exclude the possibility of a causal relationship.

Biological gradient refers to the existence of a dose-response relationship between frequency and duration of cannabis use and the likelihood of the health outcome. Satisfaction of this criterion is desirable but not necessary because there may be other patterns of relationship between cannabis use and the outcome, e.g. a threshold effect, an 'all or none', or a curvilinear relationship.

Biological plausibility: If there is no known mechanism that would explain a relationship, then we have grounds for scepticism. But if we have good evidence of association from well controlled studies, biological implausibility is not a compelling reason for rejecting a causal relationship: it may mean that existing theories are wrong, or that we need new theories to explain previously unknown phenomena.

Coherence means that the relationship is consistent with the natural history and biology of the condition. This too is desirable but not necessary: it is desirable if we have independent information that we can trust but its absence is not fatal since the other knowledge with which it is inconsistent may be in error.

1.3 Acute health effects

It is easier to make causal inferences about the acute effects of any drug (e.g. its effects on mood or thinking) than it is to make inferences about the health effects of its chronic use. It is clear in these cases that. Drug use precedes the effect; drug use and the effect typically occur closely together in time; and if the effects are not dangerous, they can be reliably reproduced in a substantial proportion of people by administering the drug under controlled conditions. All these conditions apply to the acute psychoactive effects of cannabis that are sought by recreational cannabis users (such as euphoria and relaxation). They also apply to the more common unpleasant or dysphoric effects, such as anxiety, panic and depression.

It can be more difficult to decide whether relatively rare acute experiences (such as flashbacks and psychotic symptoms) are caused by cannabis use. It may be uncertain whether these are: rare events that occur coincidentally with cannabis use; unusual effects of cannabis use that occur at much higher than usual recreational doses or that require some form of personal vulnerability; caused by other drugs which may have been taken with cannabis; or the result of interactions between the cannabis and other drug use.

1.4 Chronic effects

Causal inferences about the effects of chronic cannabis use become more difficult the longer the interval between starting to use it and the occurrence of the adverse health effects. If it takes a long time for adverse effects to develop, it may take longer for a suspicion to be raised about the relationship between cannabis use and the adverse outcome. In the case of tobacco, for example, it took three hundred years to discover that it caused cancer and heart disease and new health hazards of tobacco smoking continue to be discovered (11). The longer the time interval between cannabis use and the health consequence, the more alternative explanations of the association that there are to be excluded.

In making causal inferences about the chronic health effects of cannabis use we have a trade off between rigour and relevance in the available evidence. The most *rigorous* evidence is provided by laboratory investigations using experimental animals or preparations of animal cells and micro-organisms in which very large drug doses are administered over a substantial period of the organisms' lives. The relevance of such research to human disease, however, is often problematic.

Epidemiological studies of relationships between cannabis use and human disease are the most *relevant* in evaluating the human health effects of cannabis but this relevance is obtained at the expense of reduced rigour. Assessing exposure to cannabis and excluding alternative explanations of associations between cannabis use and health outcomes can be difficult in such studies. Uncertainty about the interpretation of human epidemiological studies affects interpretations of both 'positive' studies that find relationships between cannabis use and health outcomes and 'negative' studies which fail to find relationships.

A major problem in interpreting 'positive' epidemiological studies is that cannabis users are more likely to use alcohol and tobacco that are known to adversely affect health. Generally, the heavier the cannabis use, the more likely it is that the person uses alcohol and tobacco, as well as illicit drugs like amphetamine, hallucinogens, cocaine, and heroin (7, 12, 13). This makes it difficult to be confident that adverse health effects found in cannabis users are caused by their cannabis use (14).

A different problem arises when interpreting studies that fail to find any adverse health effects of chronic cannabis use. In the case of immunological effects, for example, the limited epidemiological evidence suggests that there are no adverse immunological effects of chronic heavy cannabis use in humans (2). Does this mean that THC has few, if any, immunological effects in humans or have the studies lacked the sensitivity to detect any such effects in humans? The answers to this question depends upon the likely magnitude of any such effects, their relationship to cannabis dose, frequency and duration of use, and the ability of studies with small sample sizes to detect them (15).

1.5 Comparing health effects of different drugs

Comparisons are often made between the public health impact of cannabis use and that of alcohol and tobacco. This impact is assessed by examining the number of individuals whose health is adversely affected by each type of drug and the severity of the health consequences for these individuals.

The major obstacle to making such comparisons is the paucity of information on the health effects of long-term cannabis use. It is nonetheless still useful to make comparisons of the adverse health effects of cannabis with those of alcohol and tobacco. These comparisons simply indicate whether or not cannabis shares the known adverse health effects of alcohol and tobacco. The reason for selecting these drugs are that they are widely used psychoactive drugs with which cannabis shares a route of administration in the case of tobacco, and which, in the case of alcohol, is also used for its intoxicating and euphoric effects. They therefore provide a useful standard of comparison when appraising the health risks of cannabis use.

1.6 An outline of the monograph

The remainder of this monograph reviews the literature on the health and psychological effects of cannabis in the following way. Chapter 2 describes 'cannabis as a drug'. It deals with the main preparations of cannabis that are used, the way in which they are typically used and the pharmacology of its major psychoactive ingredient, tetrahydrocannabinol or THC.

Chapter 3 describes the patterns of cannabis use in Australia and other developed societies, including the USA, Canada, and countries of the European Union. It describes sex and age differences in patterns of use and the natural history of cannabis use from adolescence into adulthood.

Chapter 4 describes the acute effects of cannabis. These include the positive psychological effects sought by recreational users as well as the adverse psychological effects some users experience. It also reviews evidence on the possible contribution that cannabis intoxication makes to motor vehicle accidents.

Chapters 5, 6 and 7 discuss the evidence on the adverse health effects of chronic cannabis use. Chapter 5 considers evidence on the effects of cannabis use on cellular functioning and the risks of users developing cancers. It also reviews evidence on the effects of cannabis use on immunological functioning in users. Chapter 6 discusses the possible reproductive effects of cannabis use. Chapter 7 considers the possible adverse effects that cannabis smoking may have on the respiratory, cardiovascular and gastrointestinal systems.

Chapters 8, 9 and 10 review research on adverse psychological effects that have been attributed to chronic cannabis use. These include the effects of cannabis use on motivation and the risk of developing dependence on the drug (chapter 8). Chapter 9 considers the possibility that people who use cannabis regularly over a period of years may develop cognitive impairment. Chapter 10 discusses evidence on the contribution that cannabis use may make to the precipitation and exacerbation of schizophrenia and other psychoses.

Chapters 11 and 12 consider the possible consequences of adolescent cannabis use. These chapters deal with evidence on societal concerns about the impact that adolescent cannabis use may have on the likelihood of using other illicit drugs (chapter 11) and on psychosocial outcomes, such as school performance, delinquency and mental health (chapter 12).

Chapter 13 considers the evidence on the therapeutic benefits of cannabis and cannabinoids. Chapter 14 concludes by comparing the adverse health effects of cannabis with those of alcohol and tobacco.

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2 Cannabis the drug

2.1 The cannabis plant

Cannabis preparations are obtained from the plant *Cannabis sativa,* which occurs in male and female forms. The cannabis plant contains more than 60 cannabinoids, that is, substances that are unique to the plant. The one that is primarily responsible for the psychoactive effects that are sought by cannabis users is delta-9-tetrahydrocannabinol or THC (1–3), which is found in a resin that covers the flowering tops and upper leaves of the female plant. Most of the other cannabinoids are either inactive or only weakly active, although they may interact with THC (2, 4).

The most common cannabis preparations are marijuana, hashish and hash oil. Marijuana is prepared from the dried flowering tops and leaves of the plant. Its potency depends upon the growing conditions, the genetic characteristics of the plant, the ratio of THC to other cannabinoids, and the part of the plant that is used (5). The flowering tops have the highest THC concentration with much lower concentrations in the leaves, stems and seeds. Varieties of cannabis cultivated for hemp fibre usually contain very low levels of THC. Cannabis plants may be grown to maximise their THC production by the 'sinsemilla' method in which only female plants are grown together (5).

The concentration of THC in marijuana may range from 0.5% to 5% while the 'sinsemilla' variety may contain 7% to 14% THC (6). The potency of marijuana preparations being sold in the USA has probably increased during the past several decades (6) although it has not increased 30 fold, as has been claimed in the popular media (7).

Hashish or hash consists of dried cannabis resin. It may be light brown to almost black and contain between 2% to 8% of THC. Hash oil is obtained by extracting THC from hashish (or marijuana) in oil. Its colour may range from clear to pale yellow/green, through brown to black. The concentration of THC in hash oil typically varies between 15% and 20% (8).

2.2 Routes of administration

Cannabis is typically smoked as marijuana in a hand-rolled cigarette or 'joint' which may include tobacco to assist burning. A water pipe or 'bong' is an increasingly popular way of using all cannabis preparations in Australia (7). Hashish may be mixed with tobacco and smoked as a joint or smoked in a pipe, with or without tobacco. Because hash oil is extremely potent a few drops may be applied to a cigarette or a joint, to the mixture in a pipe, or the oil may be heated and the vapours inhaled. Whatever preparation or method of smoking is used, smokers typically inhale deeply and hold their breath to ensure maximum absorption of THC by the lungs.

The oral route of administration may also be used. Hashish may be cooked in foods and eaten. In experimental research, THC dissolved in sesame oil is swallowed in gelatine capsules. In India, cannabis may be consumed in the form of 'bhang', a tea brewed from the leaves and stems of the plant.

Cannabis does not lend itself to injection because THC does not dissolve in water (Iversen, (3). Crude solutions of cannabis can be injected intravenously but they contain very little THC. They are more likely to include undissolved particles and substances that can cause severe pain and inflammation at the site of injection. Iversen has suggested that the inability to inject cannabis preparations was one of the reasons why its therapeutic use declined at the end of the nineteenth century.

Survey data on patterns of cannabis use in Australia indicates that all but a handful of cannabis users smoke cannabis (7). This is for a good reason because, as Martin and Cone have argued, the chemistry and pharmacology of cannabis dictate that it be smoked (2). Given the preponderance of smoking as the route of administration, the reader should assume that unless otherwise stated the method of ingesting cannabis is smoking.

2.3 Dosage

A 'typical' cannabis joint consists of between 0.5 and 1.0 g of cannabis that contains between 5 and 150 mg of THC (i.e. between 0.5% and 5% THC). The amount of THC delivered to the lungs in the smoke varies between 20% and 70% (2, 9); the rest is burnt or lost in sidestream smoke. The fraction of THC in the joint that reaches the user's bloodstream varies between 5% and 24% (mean 18.6%) (10). For all these reasons, it is difficult to estimate the typical dose of THC that is received when cannabis is smoked.

An occasional user only requires a small amount of smoked cannabis (e.g. 2 to 3 mg of absorbed THC) to experience a brief, pleasurable high, but a heavy cannabis smoker may consume five or more joints per day. Heavy cannabis users in Jamaica may consume up to 420 mg THC per day (11). In human laboratory research on the effects of cannabis, THC doses of 10, 20 and 25 mg have been defined as low, medium and high doses (12, 13).

2.4 Metabolism of cannabinoids

The way that cannabis is used affects the absorption, metabolism and excretion of THC. When cannabis is smoked, THC is absorbed within minutes into the bloodstream from the lungs. Orally administered THC is absorbed much more slowly, taking 1 to 3 hours to enter the bloodstream and produce its psychoactive effects (2).

After smoking, THC is metabolised first in the lungs and then in the liver where it is transformed into a number of metabolites (2). The metabolite 9-carboxy-THC is detectable in blood within minutes of smoking cannabis. It is not psychoactive. Another major metabolite is 11-hydroxy-THC. It is marginally more potent than THC and crosses

the blood-brain barrier more rapidly. It is found in very low concentrations in the blood after smoking and at higher concentrations after oral use (9). THC and its metabolites account for most of the psychoactive effects of cannabis (2).

Peak blood levels of THC occur within 10 minutes of smoking and decline to 5% of 10% of their initial level within an hour (2). The decline in THC reflects the conversion of THC to its metabolites. THC and its metabolites are highly fat soluble and concentrate in lipid-rich tissues, including the brain (14, 15). They may remain in the fatty tissues of the body for considerable periods of time, being slowly released into the bloodstream. This slows the elimination of THC from the body (2).

Research using sensitive detection techniques suggests that the half-life of THC in chronic users is 4 days on average (16, 17). Because of the slow clearance, THC and its metabolites accumulate in the body with repeated administration. Its slow release from fatty tissues into the bloodstream means that THC and its metabolites may be detectable in blood for several days. Traces of THC may persist for several weeks.

2.5 Detection of cannabinoids in body fluids

Plasma levels of THC in cannabis users vary between 0 and 500 ng/ml, depending on the THC content of the cannabis and the time since its use. Blood levels of THC may decline to 2 ng/ml an hour after smoking a low potency cannabis cigarette but it may take 9 hours to reach the same level after smoking a high potency cannabis cigarette. Such levels may persist for several days in chronic users because of the slow release of accumulated THC.

The detection of THC in blood above 10-15 ng/ml generally indicates 'recent' use of cannabis but it is not possible to estimate precisely how recent. A more precise estimate of the time of consumption is provided by the ratio of THC to 9-carboxy-THC. When the levels of 9-carboxy-THC are substantially higher than those of THC, cannabis was smoked more than half an hour ago, if the smoker was a naïve user (9, 13). Background levels of cannabinoids (particularly 9-carboxy-THC) in regular users make it difficult to estimate time since use.

Cannabinoid levels in urine are a weak indicator of recent cannabis use (18). In general, the more cannabinoid metabolites in urine, the more recent the use but it is impossible to be precise about how 'recent' (9). Only minute traces of THC are found in urine because most of the THC is excreted as metabolites in faeces and urine (19). 9-carboxy-THC can be detected in urine within 30 minutes of smoking. This and other metabolites may be detected for several days in first time or irregular cannabis users but regular users may continue to excrete metabolites for weeks and possibly months (20, 21).

Studies of cannabinoids in saliva have found that THC can be stored for at least 28 days (22). Measurement of cannabinoids in saliva may reduce the time frame for 'recent' use from days and weeks to hours because they reflect the presence of residual THC in the mouth after smoking (9, 23, 24). Salivary THC levels are correlated with subjective intoxication and heart rate (25).

Unlike alcohol where psychomotor impairment is correlated with blood alcohol level, there is no simple relationship between levels of THC (or its metabolites) in blood and impairment (18, 26). This is for two reasons: the delay between experiencing the subjective high and the appearance of THC in the blood; and large variations between different people in the level of intoxication experienced at the same blood level of THC. A consensus conference of forensic toxicologists concluded that there was not sufficient evidence for blood concentrations of THC to define a legal basis for driving a motor vehicle while under the influence of cannabis (27).

2.6 Two special concerns

2.6.1 Storage of THC

There is good evidence that with repeated dosing of cannabis at frequent intervals, THC can accumulate in fatty tissues in the human body where it may remain for considerable periods of time (Ashton (18) and see above). The storage of cannabinoids *would* be serious cause for concern if THC were a highly toxic substance which remained physiologically active while stored. THC is not a highly toxic substance and it is unlikely to have active effects while stored in body fat because it acts in receptors that are not present in body fat. One *potential* health implication of THC storage is that the release of stored cannabinoids into blood may produce unexpected symptoms of cannabis intoxication. The release of stored THC has been suggested as an explanation of 'flashback experiences' (e.g. Negrete (28); Thomas (29)). Such experiences have been rarely reported by cannabis users (e.g. Edwards (30)), and their significance is complicated by the fact that those who have reported these experiences have often used other hallucinogenic drugs.

2.6.2 Increases in the potency of cannabis

Cohen (31) claimed that research underestimates the adverse health effects of cannabis because it was largely based upon studies conducted when cannabis users used less potent forms of cannabis (0.5% to 1.0% THC) than later became available in the USA in the 1980s (3.5% THC in 1985–1986). This claim has been repeated often in the popular and scientific media (18, 32), usually asserted rather than shown and often supported by anecdotal reports of samples of cannabis containing high percentages of THC. An alleged 'thirty-fold' increase in potency has contributed to recent concerns about the health effects of cannabis in Australia (7).

There are two different interpretations of this claim: (i) that the average THC content of cannabis plants has increased; and (ii) that the average THC content of cannabis products consumed by users has increased by 10–30 times (7).

The USA is the only country that has regularly collected data on the THC content of cannabis plants over the past several decades. Claims that this data indicated that the THC content of cannabis in the USA had increased between three to seven-fold from the early 1970s to the mid 1980s have been challenged by data from independent laboratories, and because such claims relied on the assumption that the samples from the middle 1970s were representative of cannabis consumed at that time. More recent data have failed to show a 10–30 fold increase in the THC content of seizures between 1984

and 1998. At most this series shows a small increase in THC content from 3.3% in 1980 to 4.4% in 1998 (6, 33). Recent data published on the THC content of cannabis seized in New Zealand over the past 20 years has not shown any increase in average THC content (34).

2.7 Cannabinoid biology

Research during the 1990s has clarified the ways in which cannabinoids act in the human body and brain (35, 36). This research has identified 'cannabinoid receptors' and 'endogenous cannabinoids'. Cannabinoid receptors are the molecular sites in the brain and body at which the active components of cannabis, such as THC, act (36). Endogenous cannabinoids are substances that naturally occur in the human brain and body that, like THC, act on cannabinoid receptors in the brain. These include anandamide (37) and 2-arachidonyl-glycerol (2AG) (38, 39).

Two types of cannabinoid receptors, CB_1 and CB_2 have been identified. The CB_1 receptor that is found primarily in the brain is responsible for the psychological effects of THC (40). The CB_2 receptor is found in the immune system but its precise role remains unclear. CB_1 and CB_2 receptors belong to a large group of receptors found in the membranes of nerve cells that are involved in chemical signalling between nerve cells. Cannabinoid receptors have been found in the nervous system of lower vertebrates, including chickens, turtles and trout (41). This suggests that these receptors were present early in evolution, and their conservation implies that they serve an important biological function in many species including mammals (2).

The distribution of CB_1 and CB_2 receptors in the brain, immune and reproductive tissues is consistent with many of their therapeutic and recreational effects (38, 39). CB_1 cannabinoid receptors in the brain are most concentrated in brain systems that are involved in controlling mood, motor function, memory formation, food intake, pain modulation, immune, and reproductive functions).

Cannabis disrupts short-term memory in humans (see Chapter 4). This effect is consistent with an abundance of CB_1 receptors in the hippocampus, the brain region most closely associated with memory (3, 39). A high density of CB_1 receptors in the basal ganglia and cerebellum is consistent with the observation that cannabinoids interfere with coordinated movement (2). Cannabis has very little acute effect on respiratory function in humans (42, 43), which is consistent with the observation that the lower brainstem area has few cannabinoid receptors. The absence of cannabinoid receptors in the lower brainstem also explains why high doses of THC are rarely lethal (3).

2.8 Summary

Cannabis is derived from the *cannabis sativa* plant. THC is the constituent of cannabis that produces the psychoactive effects sought by recreational users. Different forms of cannabis (marijuana, heads, hash and hash oil) vary in their potency. Cannabis is

predominantly smoked in a joint or in a water pipe because this is the most efficient way to deliver THC quickly to the bloodstream and brain. THC and its metabolites can be detected in blood and urine but there is no simple relationship between these levels in blood or urine and the degree of intoxication or psychomotor impairment. THC acts on brain receptors ('cannabinoid receptors') that are also acted upon by substances that occur naturally in the brain ('endogenous cannabinoids'). Cannabinoid receptors are found in brain regions involved in control of mood, memory, and motor performance, all of which are affected by cannabis.

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3 Patterns of cannabis use

3.1 Measuring cannabis use

Most information about cannabis use is collected by surveying the general population and high school and university students. These surveys typically ask each person whether he or she has used cannabis: at any time in their lives (lifetime use), in the past year (past year use), and in the past month. Rates of weekly and daily cannabis use are low in most populations, so surveys typically only report whether the person has used cannabis in his or her lifetime or in the past year.

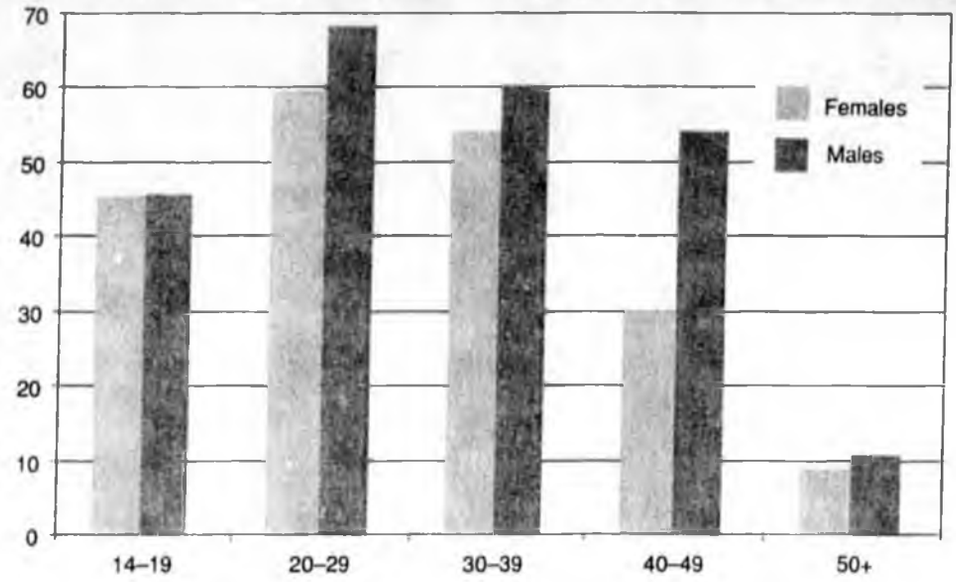
There is good evidence that carefully designed surveys provide valid information on self-reported cannabis use. O'Malley, Bachman, and Johnston (1), for example, showed that self-reported drug use in three waves of interviews of high school seniors was as reliable as self-reports of other behaviour. They have also shown that although some older adults later under-report drug use in adolescence and early adult life, under-reporting of cannabis use is quite low (2, 3). Most importantly, any small biases in self-reported cannabis use are fairly constant over time, meaning that we can be reasonably confident about *trends* in drug use from surveys (4, 5).

3.2 Cannabis use in Australia

Cannabis is the most widely used illicit drug in Australia. In 1998 39% of adults aged 15 and older reported that they had used cannabis at some time in their lives (6). Men were more likely to have used cannabis than women at all ages (44% of males vs. 35% of females) (7). Rates of cannabis use were highest among young adults: 45% of 14–19 year olds and 64% of 20 to 24 years olds reported lifetime cannabis use. Rates declined steadily with age (see Figure 1). The low rates of lifetime cannabis use among adults over the age of 50 years reflects the beginning of widespread cannabis use among young Australian adults in the early 1970s (7).

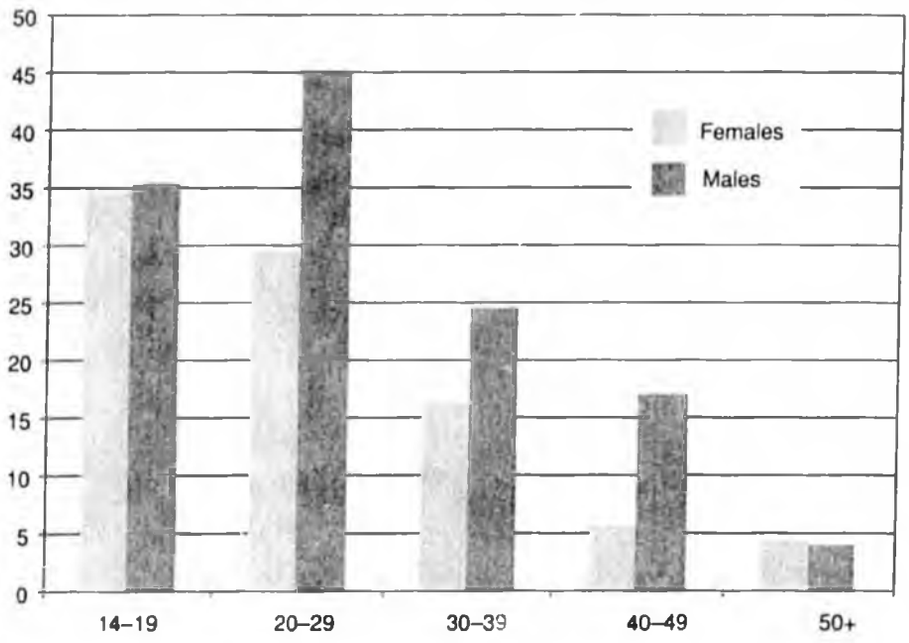
Most cannabis use is not regular. In the 1998 survey, three quarters of women and two thirds of men who had ever used cannabis either had not used in the past year or had used less than weekly (6). The proportion of users who became weekly users was 7% of women and 15% of men. Weekly cannabis use was most common among those aged 20 to 24 years, declining steeply thereafter (8).

Figure 1: Prevalence of lifetime cannabis use by age and gender, 1998 NDS survey



The rate of cannabis use in the past 12 months was 18% in the 1998 NDS. This was an increase on rates of use in previous household surveys, which found rates of 12 to 13% (9). Current use of cannabis was more common among males (21%) than females (15%) (Figure 2) but there was no difference in the youngest age group. The prevalence of current cannabis use was highest among 14–19 year olds (35%) and 20–29 year olds (37%). This is consistent with previous NDS surveys (8).

Figure 2: Prevalence of 12-month cannabis use by age and gender, 1998 NDS survey



The 1996 Australian School Student's Alcohol and Drugs Survey found that 36% of students aged 12–17 had used cannabis (10). Earlier studies of drug use among school aged youth in various Australian states conducted in the early 1990's reported rates of cannabis use between 25 to 30% (8). The 1996 school survey results suggest that there was an increase in the use of cannabis among youth during the 1990s, a finding that is supported by the NDS household surveys. The most recent national school survey found a small decline in rates of recent cannabis use among school students between 1996 and 1999 (11).

Australian cannabis users were more often males, who were under 35 years of age and more likely to be unemployed than non-users. While persons with higher education levels are more likely to have tried cannabis at some time in their lives, persons with lower levels of education are more likely to be regular users (9). Current cigarette smokers are more likely to smoke cannabis than non-smokers, and regular drinkers are more likely than occasional or non-drinkers, to be regular users of cannabis (12). Cannabis in Australia is most typically smoked, and the types of cannabis most commonly used are heads and leaf (9). The preferred mode of administration among younger users is a bong and to a lesser extent, a pipe; older users are more likely to smoke joints (13).

Surveys of drug use in the general population were not conducted in Australia until the mid 1980s. However, throughout the 1970s some market research companies included questions on cannabis use in other surveys (14). These show an increase in cannabis use in all age groups between 1973 and 1984. Among 20 to 29 year olds, for example, 23% reported having used cannabis in 1973 while the figure increased to 39% in 1984. The sharp increase in the rates of cannabis use between the 1984 market research survey and the 1985 national household survey may reflect greater anonymity given to respondents in the 1985 survey, and the different settings in which these questions were asked (in an 'omnibus' survey of consumer attitudes in 1984 and a special purpose survey about drug use and drug-related issues in 1985). There has been an increase in the percentage of Australians who report having ever tried cannabis in the NDS household surveys from 28% in 1985 to 39% in 1998.

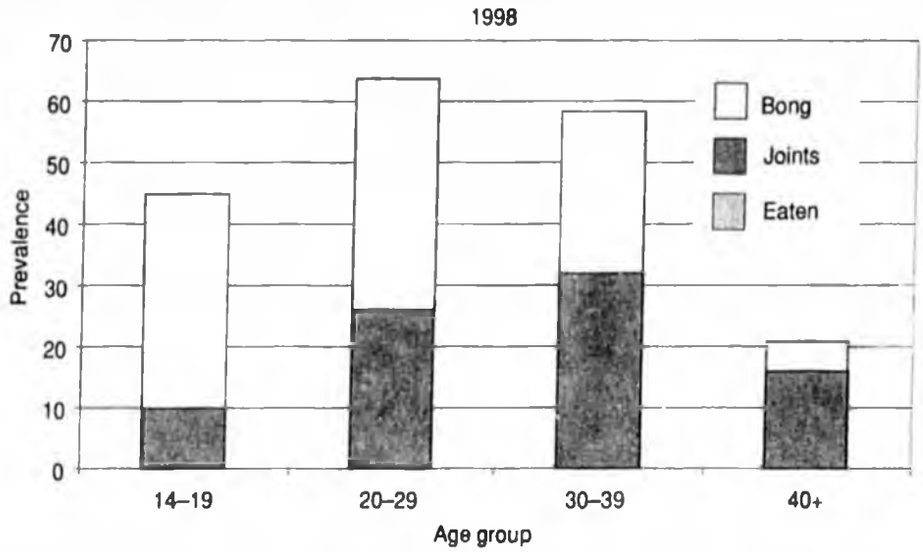
3.2.1 Changing patterns of cannabis use

Younger cannabis users now use more potent forms of cannabis at an earlier age. The 1998 NDS data show a decline in the age of initiation among younger cannabis users. One in five cannabis users (21%) born between 1940 and 1949 had initiated cannabis use by age 18, compared to 43% of those born in 1950–59, 66% of those born 1960–69 and 78% of those born in 1970–79 (15).

Earlier initiation of cannabis use increases the chances that these users will become daily or nearly daily cannabis users (16, 17). This, in turn, increases the risks of becoming dependent on cannabis and experiencing problems as a result of their use (16, 18). Levels of consumption among some adolescent cannabis users can be very high. For example, 40% of a sample of NSW juvenile offenders reported smoking 40 or more 'cones' of cannabis a week (19).

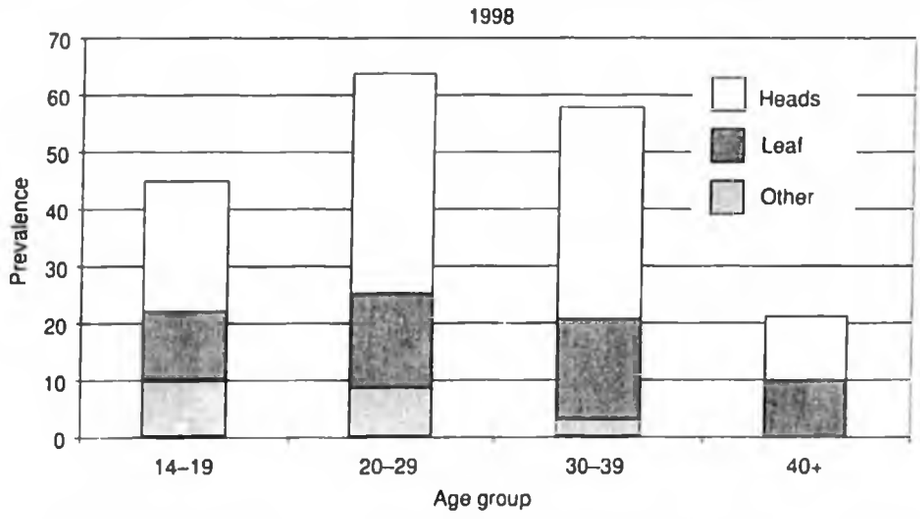
The greater expense of cannabis heads also encourages regular users to smoke them in waterpipes or 'bongs' in the belief that this maximises the delivery of THC. In the 1998 NDS Survey just over half of all persons who had used cannabis in the last year smoked 'heads' (57%) using bongs (56%). Younger users were more likely than older users to prefer bongs or pipes to joints (Figure 3) and heads to leaf, with the opposite trend in older users (Figure 4).

Figure 3: Prevalence of preference for different methods of using cannabis by age group



Source: National Drug Strategy Household Survey, 1998; Social Science Data Archives

Figure 4: Prevalence of preference of use of cannabis products according to age group



Source: National Drug Strategy Household Survey, 1998; Social Science Data Archives

All these changes in patterns of use—earlier initiation of cannabis use, greater use of more potent cannabis products such as heads, and the use of waterpipes—have probably increased the amount of THC consumed by regular cannabis users, while the concentration of THC in cannabis products has increased only marginally.

3 Cannabis use in the United States

In the United States two major surveys of illicit drug use have been undertaken since the early 1970s. The National Household Survey on Drug Abuse (sponsored by the National Institute on Drug Abuse) has surveyed household samples of adults throughout the U.S. since 1972. Since 1975, the 'Monitoring The Future' project has surveyed nation-wide samples of high school seniors, college students and young adults each year (2, 3).

3.3.1 NIDA Household Survey

NIDA has surveyed approximately 9000 persons aged 12 years and older in randomly selected households throughout the U.S. every two to three years since 1972. Since 1991, the survey has been conducted annually with a sample of over 30,000 participants (20).

In 1999, one third (35%) of the national sample reported that they had tried cannabis, 9% had used in the past year, and 5% reported that they were current users (Table 1) (21). Lifetime use increased from 11% among those aged 12 to 17 years to 59% among those aged 26 to 34 years before declining to 25% among those over the age of 35 years. Rates of discontinuation of use were high: more than two thirds of men and three quarters of women who had use cannabis at some time in their lives had not used it in the last year. Monthly cannabis use was uncommon. It was more common among men (9%) than women (6%) and most common among those aged 12 to 17 years (11%).

The NIDA Household survey series from 1974 to 1990 showed that rates of cannabis use increased throughout the 1970s, peaked in 1979, declined steadily throughout the 1980s to reach their lowest level in 1990, before increasing again in 1992.

Table 1: Prevalence of cannabis use (US National Household Survey on Drug Abuse, 1999)

	Lifetime	Past 12 months	Past month
12–17 years	18.7	14.4	7.7
18–25 years	46.8	24.8	14.8
26 + years	34.7	5.4	3.0
Total	34.6	8.9	5.1

Table 2: Trends in past month cannabis use (US National Household Survey on Drug Abuse 1974–1999)

Age	1974	1976	1977	1979	1985	1988	1990	1992	1995	1996	1999
12–17	12.0	12.3	16.6	16.3	13.2	8.1	7.1	5.3	10.9	9.0	7.7
18–25	25.2	25.0	27.4	38.0	25.3	17.9	15.0	13.1	14.2	15.6	14.8
26+	2.0	3.5	3.3								3.0
26–34				20.8	23.1	14.7	10.9	11.4	8.3	8.4	
35+				2.8	3.9	2.3	3.1	2.5	2.8	2.9	

3.3.2 The Monitoring The Future project

In this series of surveys, the prevalence of cannabis use has been estimated among secondary school students, college students and young adults. Since 1975 approximately 15,000 high school seniors have been surveyed. The college students and young adults who are surveyed each year represent a sample of those who were originally surveyed as high school seniors (about 14%) and have been followed up every two years. Since 1991 national samples of 8th and 10th grade students have also been annually surveyed.

In the 1999 survey, lifetime cannabis use increased with each higher age group but use in the past year reached a plateau in the 18 (last year of high school) to 28 year age group (Table 3). Daily use peaked at age 18, with 6% of high school seniors and 4.4% of 19 to 28 year olds reporting daily cannabis use. This is much lower than the 11% of high school seniors in the peak year of 1978 who used cannabis.

Table 3: Prevalence of cannabis use in the 1999 US Monitoring the Future Survey

	Lifetime use	12 month use	Past month use	Past month daily use
8th grade (14 years)	22.0	16.5	9.7	1.4
10th grade (16 years)	40.9	32.1	19.4	3.8
12th grade (18 years)	49.7	37.8	23.1	6.0
College	50.8	35.2	20.7	4.0
19–28 years	54.6	27.6	15.6	4.4

Because of high rates of daily cannabis use in the late 1970s, in 1982 more questions were asked about the duration of daily use. In 1982, 21% of the 12th graders reported that they had smoked cannabis daily for a month a more. This fell to 8% by 1992. Daily use has been consistently higher among males than females, and among those not planning to attend college. More than half of those who were daily users by age 18 began this pattern of heavy use by age 16. In 1993, 3% of all American 12th graders surveyed reported that they had smoked cannabis daily for two years or more on a continuous basis.

There have been rises and falls in cannabis use among American adolescents since 1975. Among 18 year olds, lifetime prevalence peaked at 65% in 1980, then fell by nearly half by the early 1990s. Use in the past year peaked at 51% in 1979 and fell to 22% by 1992. The rate of discontinuing use increased among those who had ever used cannabis (Table 4, third column), with less change in rates of discontinuation among those who had used

it 10 or more times. Most of those who ceased cannabis use had not had a great deal of experience with cannabis. The time trends in cannabis use were different from those of other drugs, suggesting that the changes in cannabis use reflected factors specific to that drug. Although most users of other illicit drugs also had used cannabis, trends in the use of other illicit drugs were independent of the cannabis-use trends.

Table 4: Trends in cannabis use among those in Year 12 (US Monitoring the Future Study, 1999)

	Lifetime use	12 month use	Discontinuation rate among those who had used cannabis	
			Ever	10 times +
1975	47	40	15	4
1980	60	49	19	5
1985	54	41	25	8
1990	41	27	34	12
1992	33	22	33	11
1993	45	36	20	8
1995	42	35	17	5

After more than a decade of declining rates of cannabis use among American secondary students, the 1992 and 1993 surveys reported that cannabis use rose sharply among 8th, 10th and 12th graders, and to a lesser extent among college students and young adults. There was an increasing initiation rate and a higher rate of continued use.

Johnston and colleagues have argued that changes in beliefs about the risks of cannabis use were responsible for the reduction in use between 1979 and 1991 and for the rise in use since 1992. They reported a strong negative correlation over time between the rates of cannabis use and the perceived risk of using cannabis and peer disapproval of use (e.g. (2, 3, 22). Between 1992 and 1996, a decrease in perceived risk, and a smaller decrease in personal disapproval of cannabis use, preceded an increase in rates of use (23).

3.3.3 The natural history of cannabis use

Bachman et al (24) have examined patterns of cannabis use from adolescence into adulthood in the Monitoring the Future data. They analysed data from 14 successive cohorts of high school seniors and college students who were followed from age 18 to 35 to assess the effect of major life transitions (such as entering college, entering full time employment, marrying and having children) on rates of use of cannabis in the past 30 days.

They found a steady decline in cannabis use from the early and mid 20s to the early 30s. The pattern for cannabis was similar to that for alcohol; it differed from tobacco use which was much more persistent. Major role transitions explained a substantial part of these changes. Use increased among those entering college but their use only caught up

with that of students who did not enter college (who used cannabis more often in high school than those who went on to college). Bigger decreases in use were seen in males and females on marriage and during pregnancy. Entering the military had a large impact on cannabis use, probably reflecting drug-testing before entry to service (4).

These findings have been confirmed in a detailed study of a single cohort of high school students that was followed from early adolescence into the middle adulthood (25, 26). This study also found that cannabis use peaked in the early 20s and declined steadily through the 20s and into the 30s. The decline was explained by the increasing societal responsibilities of marriage, children and employment. Use persisted in those who: did not enter conventional marriage (e.g. remained single or cohabited); did not enter college; and who were unemployed (see Chapter 8 below).

3.4 Cannabis use in Canada

A national telephone survey was conducted in Canada in 1994 by Health and Welfare Canada on 12,155 persons aged 15 years and older (27). Overall, 28% of the sample reported that they had used cannabis at some time in their lives, with males more likely to have used cannabis than females in all age groups. Rates of use in the past year declined with age from a high of 26% among those aged 15 to 17 years to 1.4% among those aged 45 to 54 years and 1% among those aged 55 to 64 years. Most users discontinued their use

There have been school surveys conducted in a number of Canadian provinces since the early 1970s. Adlaf and Smart (28) reviewed survey results in six of the ten provinces where surveys had been conducted between the early 1970s and the late 1980s. The most consistent trend was an increase in the prevalence of cannabis use during the 1970s followed by a sharp decline during the 1980s.

Since 1977 Ontario has conducted a series of surveys of students in grades 7, 9, 11 and 13 (corresponding to ages 10 through 19 years old) with sample sizes of between three and five thousand. The prevalence of cannabis use during the previous 12 months declined from 32% in 1979 to 14% in 1989. Declines were also reported for nine other drug types including tobacco and alcohol. Rates of illicit drug use were lower in Ontario than in the neighbouring United States. The size of the decline in rates of annual cannabis use was greater than for other substances (28). The Ontario surveys also found, like the U.S. surveys, that the perceived health risks of cannabis use increased as rates of use declined (28). Since the beginning of the 1990s there has been an increase in rates of cannabis use in the past year among Ontario high school students, from 12% in 1991 to 29% in 1999 (29). Comparison of trends in cannabis use in Canada has found the same pattern as reported in the USA, namely, a decline throughout the 1980s, followed by an increase in the early 1990s (30).

3.5 Cannabis use in Europe

Few European countries have undertaken regular community or high school surveys of cannabis and other illicit drug use. Those that have done so (e.g. Denmark, France, the Netherlands, Switzerland, and the United Kingdom) all reported increases in rates of cannabis use in the early 1990s (31). In all cases, the prevalence of current use was substantially less than lifetime use, indicating that most users stopped their use. Rates of current use were highest among those aged 15 to 24 years.

The Pompidou Group (32) examined illicit drug use among high school students in Belgium, France, Greece, Italy, Netherlands, Portugal, and Sweden (using a sample from the USA as the comparison). The study found that the rates of use of almost all illicit drugs were two or more times higher in the US sample. In the European samples, cannabis had been used at least once by between 10% and 36% of the older student population, and had been used in the past 30 days by between 3% and 14% of the European students as against 19% of the US students. Cannabis was used on a near daily basis by 1% or less of European samples compared with 3% in the US.

In 1992 in the Netherlands, a large national survey of drug use was undertaken involving over 10,000 students aged 10–18 years (33). About one third of males and one fifth of females had used cannabis at some time in their lives. Data from three national school surveys in 1984, 1988 and 1992 showed large increases in use between 1988 and 1992, particularly among males.

In 1997 the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA) reported rates of lifetime cannabis use among adults and adolescents in household surveys in 9 countries and among high school students in 14 countries (34). Rates of lifetime use among adults varied from a high of 31.3% in Denmark to a low of 3.6% in a German mail survey. Rates among young adults varied between a high of 43% in Denmark to a low of 6% in Germany. Rates of use in the past year were available in fewer countries because of the low prevalence of this pattern of use, with rates varying between 1% in Sweden (for all illicit drugs combined) to a high of 21% in the United Kingdom (34). The school surveys showed higher rates of lifetime use, with a range between 41% in the United Kingdom and a low of 3% in Spain (34).

Smart and Ogborne (35) have recently analysed survey data on illicit drug use among students in 36 countries circa 1995. Most of these countries were European and developed industrialised societies. The highest rates of lifetime use of cannabis were in Britain. The rate was 53% in Scotland, followed by 41% in the United Kingdom and 33% in Wales. Then followed the USA (32%), Australia (31%) and the Netherlands (22%). Table 5 shows estimates produced by the EMCDDA in 2000.

Table 5: Prevalence of cannabis use in recent surveys in European countries

	Lifetime use (young adults)	12-month use (young adults)	Lifetime use (all adults)	12-month use (all adults)
Belgium	9.2	3.6	5.8	1.5
Denmark	43.0	6.0	31.3	3.3
Finland	17.5	6.3	9.7	2.5
France	25.7	8.9	16.0	4.7
E Germany	7.8	4.5	4.2	2.3
W Germany	20.1	7.8	13.4	4.5
Greece	19.7	8.8	13.1	4.4
Ireland	-	-	6.4	-
Netherlands	27.3	9.8	18.1	5.2
Spain	31.8	14.2	22.2	7.6
Sweden	16.0	2.0	13.0	1.0
United Kingdom	42.0	23.0	25.0	9.0

Taken from EMCDDA (2000)

These data suggest that, with the exception of the United Kingdom and Denmark, rates of cannabis use by young people in Europe is probably much lower than that in the USA. This has been confirmed in the recent European School Survey Project on Alcohol and Drugs (EPSAD) (36) which used the Monitoring the Future instrument to survey drug use in 95,000 year 10 school students in 30 participating countries. It found that the average rate of lifetime cannabis use in Europe was much lower (17%) than in the USA (41%). Rates in individual countries ranged between 1% in Romania and 35% in the Czech Republic, France and the United Kingdom (36).

3.6 Cannabis use in other regions

There is limited survey data on rates of cannabis use in other parts of the world (37). Surveys have been reported from different countries but their results have often been reported in ways that make it difficult to compare rates. In many cases these data provide only crude rates of cannabis use, survey methods are poorly reported, and it is sometimes unclear whether rates are lifetime or recent cannabis use (37). The limited data from developing countries in Africa, the Caribbean, Asia and South America suggest that rates of cannabis use are much lower in these countries than in Europe and English-speaking countries (37).

3.7 Correlates of cannabis use

Age: First use of cannabis typically begins in the teens and the heaviest rates of use occur in the early 20s. Rates of cannabis use remain relatively high during the early 20s but declines thereafter. Chen and Kandel (26) found that the majority of young adults who experimented with cannabis had done so by age 18 and Bachman et al (24) have found that rates of use decline steadily from the mid 20s into the early 30s.

Gender: Rates of cannabis use in the lifetime, the past year and the past week are consistently higher among males than females (2, 3, 8, 28). Daily use and long-term daily use are much more common among males (2, 3).

Income: A positive relationship has been found between income in adolescence and early adult life and cannabis use (9), with those earning more money more likely to report cannabis use. In the United States, Johnston (22) also reported that daily cannabis use correlated positively with income and hours worked on a paid job.

Socioeconomic Status: The relationship between cannabis use and socioeconomic status (SES) is weak. Higher rates of cannabis use are sometimes found among lower SES individuals but in the past two decades there has been no relationship between parent's education and cannabis use among 12th grade students in the United States, with the exception that the group with lowest parental education had slightly lower cannabis use than the others (2, 3). That difference may be better explained by differences in income during adolescence rather than by social class.

Ethnicity: Information on the relationship between ethnicity and cannabis use is limited. Ethnic differences in one country may not generalise to others and small sample sizes often make ethnic comparisons unreliable. Even in the very large Monitoring the Future survey, samples from several years have to be combined to make reliable comparisons between the three largest ethnic groups (2, 3, 38). These show that African-American students have lower rates of use in all grades than White or Hispanic students. Hispanics, on the other hand, tend to have the highest rates of use in the early grades, before the rates of school drop-out increase.

Availability: In general, and all other things being equal, the more freely available a drug is, the higher its use in the population. This hypothesis has been broadly supported in the case of alcohol consumption, where the larger the number of licensed outlets and the longer the hours of trading, the higher the levels of community alcohol consumption and alcohol-related problems (39, 40). There is very little evidence to rigorously test this hypothesis in the case of cannabis use. Self-reports from surveys on how easy it is to obtain cannabis (2, 3) have shown very little change over long periods of time for cannabis in the USA.

3.8 Summary

Patterns of cannabis use have been most extensively studied in developed societies such as the USA, Canada, Australia and some European countries. The limited data in Europe shows lower rates of use than in Australia, Canada and the USA. The highest rates are in the United Kingdom, Denmark and France. The limited data from developing countries suggest that Africa, the Caribbean, Asia and South America have much lower rates of cannabis use than Europe and English-speaking countries.

The USA, which has systematically collected survey data on cannabis and other drug use since 1975, has documented long waves of cannabis consumption among young people. Rates of cannabis use increased through the 1970s in the USA, peaked in 1979 and

declined throughout the 1980s until 1991. Rates of use increased sharply in 1992 and have continued to increase throughout the 1990s with a leveling out in the late 1990s. A rising trend in cannabis use during the early 1990s has been reported in Australia, Canada, the Netherlands, Norway and Sweden. The 'natural history' of cannabis use in studies conducted in the USA is for use to start in the mid to late teens, reach its maximum in the early 20s and decline in the mid to late 20s. A minority of cannabis users continue to use into their 30s. Marrying and having children substantially reduce rates of cannabis use.

A substantial minority of young people in Europe, North America and Australia (and during some periods in the USA and Australia, the majority) have tried cannabis at least once in their lives. Rates of regular cannabis use are much lower. Most cannabis users discontinue their use. Lifetime and recent cannabis use are higher among males than females, and highest among young adults in their early 20s.

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4 The acute effects of cannabis

4.1 Psychological effects

The effects of cannabis depend upon the dose received, the mode of administration, the user's prior experience with cannabis, any concurrent drug use, and the 'set and setting'—the user's expectations, attitudes towards the effects of cannabis, their mood state, and the social setting in which it is used (1). The main reason why most young people use cannabis is to experience a 'high': mild euphoria, relaxation and perceptual alterations, including time distortion, and the intensification of ordinary experiences, such as eating, watching films, listening to music, and engaging in sex (1, 2). When used in a social setting, the 'high' may be accompanied by infectious laughter, talkativeness, and increased sociability.

Cognitive changes include impaired short-term memory and attention. These make it easy for the user to become lost in pleasant reverie and difficult to sustain goal-directed mental activity (3, 4). Motor skills, reaction time, motor coordination and many forms of skilled psychomotor activity are impaired while the user is intoxicated (1, 4).

Some users report unpleasant experiences after using cannabis. These include anxiety, panic, a fear of going mad, and depression (5–7). These are often reported by users who are unfamiliar with the effects of cannabis (7), and by some patients given THC for therapeutic reasons (8). More experienced users may report these effects after swallowing cannabis because its effects may be more pronounced and of longer duration than they usually experience after smoking. These effects can be prevented by preparation of users about the effects they may experience and they can be managed by reassurance and support (5, 7). Psychotic symptoms, such as delusions and hallucinations, are very rare experiences that may occur at very high doses of THC, and perhaps in susceptible individuals at lower doses (5–7) (see Chapter 10 below).

4.2 Physical effects

The most immediate effect of smoking cannabis is to increase the heart rate by 20% to 50% within a few minutes to a quarter of an hour of smoking cannabis (9–11). Changes in blood pressure also occur. These depend upon posture: blood pressure is increased while the person is sitting, and decreases while they are standing. A sudden change from lying down to standing up may produce postural hypotension and a feeling of 'light-headedness' and faintness that is often the earliest indication of intoxication in naive users (12). In healthy young users these cardiovascular effects are unlikely to be of any clinical significance (11). They may amplify anxiety if the cannabis-induced palpitations and feeling faint are misinterpreted as symptoms of serious misadventure.

4.2.1 Toxic dose levels

THC is the component of cannabis that has the highest toxicity in animals. The cause of death is cessation of breathing or the heart, if breathing is assisted (13). Because tolerance develops to its effects, the toxic dose of THC depends upon the amount by which a dose exceeds the customary dose (14). Laboratory studies in humans of daily dosing of high levels of THC over weeks have demonstrated tolerance to mood effects, heart rate changes, decrease in skin temperature, increased body temperature, and impaired performance on psychomotor tests (15).

There are no reported cases of human deaths attributed to cannabis toxicity (16, 17). With many drugs the toxic dose gets smaller as one moves from mice, rats, monkeys and dogs to humans. With THC, by contrast, humans are probably much *less* susceptible to the acute toxicity of THC than animals. For example, the dose of THC which kills 50% of animals when administered intravenously is 40 mg/kg in the rat but it is 130 mg/kg in the dog and monkey (13). Extrapolation from the animal evidence suggests that the lethal human dose of THC is at least as high as, and probably higher than, that observed in the monkey. This means that the estimated toxic dose of THC in humans is so large, e.g. 4000 mg (18), that it is unlikely to be easily achieved by recreational users.

4.3 Psychomotor effects

A major societal concern about cannabis intoxication is that it may impair the psychomotor performance of automobile drivers, increasing the risk of accidents in cannabis users who drive a car while intoxicated. Individuals who drive while intoxicated with alcohol are dangerous to others in proportion to how intoxicated they are (19). It has been more difficult to decide whether cannabis intoxication impairs psychomotor performance in a similar way to alcohol.

4.3.1 Effects of cannabis on psychomotor tasks

Simple reaction time is not reliably affected by cannabis (20, 21). In choice reaction time tasks, in which the response is conditional upon the occurrence of a stimulus in the presence of another discriminant stimulus (such as the pitch of a tone), reaction time is usually slower after using cannabis (22, 23).

The performance of concurrent tasks is almost always adversely affected by cannabis, although the effects on the component tasks are not always consistent (24–28). In studies of concurrent tasks subjects are asked to do one task which requires continuous attention, typically tracking, while discriminating between significant stimuli that occur sporadically and non-significant stimuli that occur more frequently.

4.3.2 Effects of cannabis on simulated driving and flying

In simulated driving tasks subjects use skills similar to those involved in driving a car under laboratory conditions which have been designed to emulate the performance characteristics of a car. These simulations have two major advantages (29): cannabis users can be tested after taking large doses of cannabis, and they can be placed in simulated emergency situations which test their level of impairment. It would be unethical to do either of these things on the road. The difficulty with simulator studies lies in achieving fidelity to the conditions of on-road driving.

Smiley (29, 30) who critically reviewed research on the effects of cannabis on simulated driving has argued that the early studies which showed fewer effects than later studies suffered because of their unrealistic car dynamics. Later studies that used more realistic driving simulators have shown impairments of lane control after cannabis use. Some of the studies have also shown reductions in risk-taking as manifested in slower speeds, and maintenance of a larger distance from the car in front in following tasks (30).

A smaller number of simulator studies have been done on the effects of cannabis on flying skills. Janowsky et al (31) found substantial increases in errors in keeping the plane at the proper altitude and heading during a simulated flight after pilots had taken cannabis. Yesavage et al (32) originally reported that a simulated flying task was impaired up to 24 hours after smoking cannabis but this study did not include a control group. A later study with a control group (33) failed to replicate this result and only found an effect 1 to 4 hours after smoking. A third study that also included a control group (34) failed to show impairments in performance up to 24 hours after smoking cannabis. Although much has been made of the original findings (despite the failure to replicate them), the effects were very small and of uncertain significance for flying safety. Jones (35) has argued that the use of cannabis by pilots 24 hours before flying may be more an indicator of poor judgement than a risk because of residual psychomotor effects of cannabis.

4.3.3 Effects of cannabis on driving on road courses

A number of studies have been done on the effects of cannabis on driving cars around off road courses. These studies have found that cannabis has modest effects by comparison with alcohol. An early study by Hansteen et al (36) showed that a moderate dose of alcohol (approximately 0.07 BAC) or THC (5.9 mg) impaired driving on a traffic-free course, with driving speed decreased after using cannabis but not alcohol. Smiley et al (37), using a different type of course, found that reaction time to signal stimuli was increased by a combination of cannabis and alcohol. Klonoff (38) studied driving on a closed course, and in city traffic, after a placebo and two doses of smoked cannabis (4.9 and 8.4 mg THC). Driving on the closed course was impaired by both doses. Driving in traffic, however, was not significantly affected. Sutton (39) also found that cannabis had little effect on actual driving performance.

Peck et al (40) recorded performance on a range of driving tasks on a closed circuit on four occasions after the administration of placebo, up to 19 mg of smoked THC, 0.84 g/kg of alcohol, and the combination of both drugs. On most individual and derived composite measures, cannabis impaired performance. The effects of cannabis on driving performance were less than those of alcohol.

A recent series of on road studies by Robbe and colleagues (41, 42) found modest impairment of driving skills after cannabis on actual driving on either a driving course without traffic, on a highway or in urban traffic. They found that drivers were aware of their intoxication after using cannabis and took steps to minimise its impact on their driving by slowing down (41).

The effects of cannabis use on on-road driving have been smaller than the effects of intoxicating doses of alcohol (29, 30). Cannabis use has consistently made drivers slow down (30). This contrasts with the typical increase in speed when drivers are intoxicated

by alcohol. The compensatory behaviour of cannabis users may explain the comparatively small effects of cannabis intoxication in on road driving studies. For ethical reasons on road studies have not been able to test the response of cannabis-intoxicated drivers to emergency situations in which there is less opportunity to compensate for impairment. The few studies which have simulated this situation (e.g. by measuring reaction to other tasks while driving) have shown that cannabis use impairs emergency decision-making (29, 30).

4.3.4 Studies of cannabis use and accident risk

It is unclear whether cannabis use increases the risk of being involved in motor vehicle accidents. Surveys (42, 43) have found that the majority of cannabis users have driven after using cannabis, despite being aware of impairment (38, 44). But epidemiological studies of accident fatalities and injuries have not definitively shown that cannabis users are more likely to be involved in motor vehicle or other accidents. This contrasts with the role of alcohol intoxication in accidents where case-control studies have shown that persons with blood alcohol levels indicating intoxication are over-represented among accident victims by comparison to drivers who are not involved in accidents (45). The lack of the evidence in the case of cannabis reflects major difficulties in obtaining the necessary evidence to assess its role (19).

There are a substantial number of studies of the prevalence of cannabinoids in the blood of drivers who have been involved in motor vehicle accidents (see Chesher (19) and McBay (46) for reviews). Studies of accident fatalities tested post-mortem have found that 4% to 37% of blood samples contained cannabinoids, most often in combination with blood alcohol levels (BAC) indicative of intoxication (e.g. (47–49). An Australian study of 1045 fatalities (50, 51) found cannabinoids in the blood of 11% of drivers, 35% of whom also had BACs indicative of intoxicating doses of alcohol. Similar findings have been reported in studies of Californian motorists tested on suspicion of impairment by the Highway patrol (52) and in a prospective study of trauma patients (53).

These findings are difficult to evaluate for a number of reasons. First, it is not clear that drivers with cannabinoids are over-represented among accident victims because we do not know how many drivers who have not been involved in accidents have cannabinoids in their blood (54). Finding a rate of 35% of accident victims with cannabinoids in their blood may seem high but so is the rate of cannabis use among young males, the group who are most likely to be involved in motor vehicle accidents (53). Second, the presence of cannabinoids in blood levels does not necessarily mean that a driver was intoxicated by cannabis at the time of an accident (55) (see Chapter 2 above). Third, it is difficult to attribute an accident to cannabis when drivers with cannabinoids in their blood also have high blood alcohol levels (19, 46).

'Culpability analysis' has been developed to address these issues (54). In these analyses, a researcher decides which driver was 'culpable' for an accident using information about the circumstances of the fatal crash but excluding information on their alcohol and drug use. Drivers with no alcohol or other drugs in their blood are used as the control group to see whether cannabis and other drugs increase driver culpability. A common problem with these analyses is that the culpability of drug-free drivers is often high. This makes it difficult to detect an increase in culpability among drivers with alcohol, cannabis and other drugs in their blood.

Most culpability analyses have shown increased culpability among drivers with intoxicating levels of alcohol in their blood (19, 56). Drivers who have only had cannabis present have been in the minority because most also have intoxicating doses of alcohol (19, 56). There has been no evidence of an additive effect of alcohol and cannabis in these analyses despite the fact that laboratory studies suggest that the impairments produced by alcohol and cannabis are additive (19). These findings have been replicated in two Australian studies that used culpability analysis to examine the role of cannabis in fatal (51) and non-fatal motor accidents (50, 57, 58). There was a strong relationship between alcohol level and culpability in each study but neither study found any relationship between THC and culpability.

A different approach has been used by Gieringer (59), who estimated the proportion of drivers who might be expected to have blood and urine samples positive for cannabinoids from US household surveys. He estimated that cannabis users were 2 to 4 times more likely to be accident victims than non-cannabis users. Cannabis users who also used alcohol were even more likely to be over-represented among the victims of motor vehicle accidents.

4.3.5 Other epidemiological data on accidental injury

There is other suggestive evidence that cannabis use may increase the risk of accidents. Two surveys of self-reported accidents among adolescent drug users found a relationship between self-reported cannabis use and involvement in accidents. Cannabis smokers were approximately twice as likely to report being involved in accidents than non-cannabis smokers (60, 61).

Two studies of deaths among cannabis users provide suggestive evidence of an association between cannabis use and accidents (62, 63). Andreasson and Allebeck reported mortality over 15 years among 50,465 Swedish military conscripts. They found that men who had smoked cannabis 50 or more times by the age of 18 had an increased risk of premature death (Relative Risk (RR) = 4.6). Motor vehicle accidents accounted for 26% of these deaths and 7% were other accidents (e.g. drownings and falls). The increased risk was no longer statistically significant after statistical adjustment for antisocial behaviour and alcohol and other drug use in adolescence (62).

Polen et al (63) compared health service use by 450 people who did not use cannabis, and 450 persons who were daily smokers of cannabis only, who were screened by Kaiser Permanente Medical Centers between July, 1979 and December, 1985. They found an increased use of medical care by cannabis-only smokers for accidental injury over one to two years of follow-up, with cannabis users who were the heaviest alcohol users showing the highest rates of use. Sidney et al (64) reported death rates after 10-years among 65,171 members of the Kaiser Permanente Medical Care Program aged between 15 and 49. The sample comprised 38% who had never used cannabis, 20% who had used less than six times, 20% who were former users, and 22% who were current users. Regular cannabis users had a slightly increased rate of premature death (RR = 1.33) but this was explained by increased deaths caused by AIDS in men, probably because cannabis use was more common among male homosexuals than male heterosexuals.

4.4 Summary

The major adverse acute effects of cannabis use are anxiety and dysphoric experiences in a substantial minority of cannabis users. The risks of fatal overdose are very small, with no deaths reported in the medical literature.

Cannabis adversely affects the performance of a number of psychomotor tasks in a way that is related to dose and the difficulty of the task. The acute effects on psychomotor performance of cannabis in doses used recreationally are similar to but smaller than those of intoxicating doses of alcohol. Alcohol and cannabis also differ in their effects on user's willingness to take risks when driving. Persons intoxicated by cannabis engage in less risky behaviour than persons intoxicated by alcohol because they seem to be more aware of their impairment.

It has been difficult for technical and ethical reasons to decide whether the impairment produced by cannabis intoxication increases the risk of motor vehicle accidents. There is reasonable evidence from studies of cannabinoid levels in accident victims, and the few epidemiological studies, to suggest that driving after using cannabis probably increases the risk of motor vehicle accidents. The increased risk may be of the order of 2 to 4 times but it is difficult to rule out the possibility that it is the result of the combined use of cannabis and alcohol.

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