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5 Cellular and immunological effects of cannabis use

5.1 Is cannabis a potential cause of cancer?

Cannabis could be a cause of cancer if the cannabinoids it contains (or substances produced when it is burnt) produce genetic mutations in the user's somatic cells (such as those in the lung) (1). There is only weak evidence that THC is 'mutagenic' in this sense. THC can produce changes in cellular processes in animal cells in the test tube (2) but these changes probably delay or stop cell division rather than produce cellular changes that may lead to cancer (1).

There is no evidence that THC and other cannabinoids produce mutations in microbial tests of mutagenicity, such as the Ames test (1, 3). There is inconsistent evidence on whether cannabinoids produce breaks in chromosomes (3) but if they do, these changes are unlikely to cause cancers (1) because chromosomal abnormalities are more likely to kill the affected cell than to produce malignant transformation and proliferation (1). A recent study in rats and mice found no evidence that THC caused cancer (4).

Cannabis ***smoke*** is mutagenic in the test tube, and hence is potentially a cause of cancer (i.e. carcinogenic) (1, 3, 5). Cannabis smoke produces chromosomal aberrations, is mutagenic in the Ames test (6) and causes cancers in the mouse skin test (1). The fact that it is cannabis *smoke* that is carcinogenic (6) suggests that any cancers caused by cannabis smoking are most likely to occur in organs that receive long term exposure to cannabis smoke and the tars it contains, such as the lung, the upper aerodigestive tract (mouth, tongue, oesophagus) and the bladder (1).

5.2 Is cannabis smoking a cause of aerodigestive tract cancers?

There are good reasons for suspecting that cannabis may cause cancers of the lung and the aerodigestive tract (the oropharynx, nasal and sinus epithelium, and the larynx). First, tobacco is a cause of respiratory cancer (7) and cannabis smoke contains many of the same cancer-causing substances as tobacco smoke (8). Second, chronic cannabis smokers show many of the pathological changes in lung cells that precede the development of cancer in tobacco smokers (9, 10).

Third, cancers of the upper aerodigestive tract have been reported in young adults who have been chronic cannabis smokers (11–15). In many cases these were also cigarette smokers and alcohol consumers but Caplan and Brigham reported two cases of cancer of the tongue in men aged 37 and 52 years (12), neither of whom smoked tobacco or consumed alcohol. A history of long-term daily cannabis use was their only shared risk factor. These reports raise a suspicion but provide limited support for the hypothesis that

cannabis use is a cause of upper respiratory tract cancers. They do not compare rates of cannabis use in cases and controls, cannabis exposure has been assessed retrospectively and in the knowledge that the user has cancer; and they do not control for confounding factors such as alcohol and tobacco use.

Two recent controlled studies have produced inconsistent results. Sidney et al (16) studied cancer incidence during an 8.6 year follow up of 64,855 members of the Kaiser Permanente Medical Care Program (KPMCP). Study participants were asked about cannabis use during medical screening between 1979 and 1985. Their average age at entry was 33 years and they were followed until: death, a diagnosis of cancer or HIV/AIDS, exit from the KPMCP or 31 December 1993 (a mean of 8.6 years). At study entry 38% had never used cannabis, 20% had used it less than 6 times, 20% were former users, and 22% were current cannabis users. Data were collected from a cancer registry and the California mortality data system.

There were no more cases of cancer among those who had ever used cannabis or who were current cannabis users than among those who had not used cannabis at study entry. There were more tobacco-related cancers among tobacco smokers (regardless of cannabis use) but no more among cannabis smokers. Males who had ever smoked cannabis had an increased risk of prostate cancer (RR = 3.1) and so did males who were current cannabis smokers (RR = 4.7) (16).

Zhang et al (17) compared rates of cannabis use among 173 persons with primary squamous cell carcinoma of the head and neck and 176 controls who were blood donors matched on age and sex from the same hospital. Cases were more likely to have used cannabis than controls (14% and 10% respectively), with an odds ratio for cannabis smoking of 2.6 after adjusting for cigarette smoking, alcohol use and other known risk factors. The cases with cancer smoked cannabis more often and for longer than the controls. The relationship between cannabis smoking and these cancers was stronger among adults under the age of 55 years (Odds Ratio (OR) = 3.1). There was a suggestion that cancer cases were more likely to smoke both tobacco and cannabis than controls (17).

How do we reconcile the negative findings of the Sidney et al study with that of Zhang et al? The persons studied by Sidney et al were too young (average age of 43 at follow up) to see many excess cases of cancer attributable to cannabis smoking. The chance of Sidney et al finding cancers was further reduced because only 22% were cannabis users at study entry.

There is as yet no evidence that regular cannabis smoking causes cancers of the lungs and lower respiratory tract of the type caused by cigarette smoking (10). Studies of respiratory cancers would be timely since cannabis users in the post-War birth cohorts are reaching the age of 60 years when the incidence of all cancers steeply increases. A longer follow-up of the Sidney et al cohort may reveal whether cannabis smoking causes respiratory cancers.

5.3 The public health impact of cancers caused by cannabis smoking

On current patterns of use, cannabis smoking will cause very few respiratory cancers, even if the risks of *daily* cannabis smoking are comparable to those of daily tobacco smoking (18). This is because in Western societies there are many more daily tobacco (25–30%) than daily cannabis smokers (1–3%) (19), most cannabis smokers stop in their mid to late twenties (20), and the 1% or less who smoke cannabis daily over decades typically smoke 1 to 3 cannabis cigarettes per day rather than 10 to 30 tobacco cigarettes a day (21). Among this minority of users, prolonged use of cannabis into the fourth and later decades may increase the risk of respiratory cancer, especially among tobacco smokers who also smoke cannabis.

5.4 Is cannabis smoking during pregnancy a cause of childhood cancers?

Cannabis smoking has also been linked to cancers in children born to mothers who used cannabis during their pregnancy. Three case control studies have examined cannabis use as a risk factor for childhood cancers, along with a range of other risk factors. There was no prior reason to expect cannabis use to be related to these cancers, as there was with respiratory cancers.

Maternal cannabis use and childhood cancer were associated in a case-control study of Acute Nonlymphoblastic Leukemia (ANLL), a rare form of childhood cancer (22, 23). The study was designed to assess the relationship between this childhood cancer and maternal and paternal environmental exposures to petrochemicals, pesticides and radiation. Maternal cannabis use was assessed before and during pregnancy as one of many variables to be statistically controlled when analyzing the relationship between ANLL and maternal and paternal environmental exposures.

A strong association was found between maternal cannabis use and ANLL. The mothers of cases were 11 times more likely to have used cannabis before and during their pregnancy than mothers of controls. The relationship persisted after statistical adjustment for other risk factors. An alternative explanation is that because reports of cannabis use were obtained after the diagnosis of the ANLL, mothers of children with ANLL may have been more likely to report cannabis use than were mothers of controls. The authors did find that the rate of cannabis use among the controls in this study was much lower than among controls in other studies. When the rate of cannabis use among controls was adjusted upwards there was a reduced but still significant three-fold increase in risk.

Two other case-control studies have reported an increased risk of rhabdomyosarcoma (24) and astrocytomas (25) in children born to women who reported using cannabis during their pregnancies. Neither planned to study the association between childhood cancer and maternal cannabis use. In each case, cannabis use was one of a large number of variables that were to be controlled for in statistical analyses of the relationship between the exposure of principal interest and the childhood cancer.

Trends in the rates of these cancers suggest that these studies may have produced chance results. There was no increase in the rate of any of these cancers between 1979 and 1995 (26). The rate of ANLL, for example, remained steady during this period (27). The same was true of soft tissue sarcomas (which include rhabdomyosarcomas) (28). Cancers of the brain (about 52% of which are astrocytomas) did increase in incidence between 1979 and 1995 (29) but in a way that is more likely to reflect improved diagnosis than maternal cannabis use. The rate of these cancers increased abruptly in 1985, after Magnetic Resonance Imaging became widely available in the USA, and remained stable thereafter (29).

5.5 Immunological effects

Tobacco smoking suppresses humoral and cell-mediated immunity so it is reasonable, given the similarities between cigarette and cannabis smoke (30), to expect that cannabis smoke suppresses immunity (2). Cannabinoid receptors are also expressed in some immune cells (Kamminski, 1998) so THC may influence the immune system. If cannabinoids have immunosuppressive effects then their therapeutic use may be limited in patients with impaired immune systems. This could preclude their use as anti-emetic agents in cancer chemotherapy and as appetite stimulants and mood enhancers in patients with AIDS.

There are difficulties in deciding whether cannabis impairs the immune system in humans. First, most studies have been conducted on whole animals and in animal and human cell cultures that have been exposed to cannabis smoke or cannabinoids. The relevance of these studies to humans is limited by the fact that they used very high oral doses of THC (31). Second, there have been very few epidemiological studies of immune system functioning and disease susceptibility in heavy chronic cannabis users (31).

5.5.1 Effects of cannabinoids on humoral immunity

The effect of cannabinoids on humoral immunity has been assessed by measuring their effect on animal and human B-cell responses to sheep red blood cells. Cannabinoids do not consistently alter B-cell functioning (32). While cannabinoids consistently impair the B-cell responses in mice, no such effects have been observed in humans, and the few positive studies have produced results that are within the normal range (32).

Antibodies have been formed to THC in animals (31) and there are clinical reports in humans that cannabinoids exacerbate allergies and that allergy to cannabinoids can develop in humans (31). Hollister (33), however, has argued that although a few persons may become truly allergic to cannabinoids it is more likely that these are rare allergic reactions that are due to contaminants (e.g. bacteria, fungi, moulds, parasites, worms, chemical) found in cannabis.

5.5.2 Effects of cannabinoids on cell-mediated immunity

Studies of the effects of cannabinoids on T-cells and macrophage numbers have been mixed, with some showing reductions (2) while others have not (34). The evidence is also mixed on the effect of cannabinoids on T-cell functioning. A number of the earliest

studies suggested that T-cells from chronic cannabis users were less responsive but later laboratory studies of chronic heavy dosing in humans (35) have failed to replicate these results. Studies exposing human T-cells to cannabinoids have also produced mixed results while animal studies have showed a decreased T-cell response (32).
In a review of the literature published in this field in the 1990s, Klein (31) concluded that THC affected the function of immune cells including lymphocytes, macrophages, and polynuclear cells in the test tube but relatively high drug concentrations were required, the effects were not related to psychoactivity, and they were reversible.

5.5.3 Effects of cannabinoids on host resistance

Studies in mice and guinea pigs have suggested that high doses (200 mg/kg) of THC reduce resistance to infection (36–39). A consistent finding in humans has been that exposure to cannabis ***smoke*** adversely affects alveolar macrophages, the immune cells in the respiratory system that comprise the first line of defence against micro-organisms which enter the body through the lungs (5). Studies of these cells in cannabis smokers have shown abnormalities (40), and exposure of alveolar macrophages to cannabis smoke impairs their ability to inactivate bacteria (5, 32), and a fungus (41). It is the noncannabinoid components of cannabis smoke that produce these effects (5).

5.5.4 The human significance of the immunological effects of cannabinoids

The animal evidence is reasonably consistent that cannabinoids impair cell-mediated and humoral immunity and several animal studies have found decreased resistance to a bacteria and virus. However, the doses required to produce these immunological effects in animals are much higher than the doses used by humans (1). Human users may also develop tolerance to any immunological effects of cannabinoids, which may reduce the small effects projected from animal studies. Given the large number of cannabinoid effects to which tolerance has been shown to develop it would not be surprising if this were also true of its immunological effects.

The limited human evidence is mixed. A small number of studies that suggest that cannabis use impairs immunity have not been replicated by others. Munson and Fehr (32) concluded that there was 'no conclusive evidence' that cannabinoids impaired functioning of T-lymphocytes, B-lymphocytes or macrophages, or reduced immunoglobulin levels in humans. There was 'suggestive evidence' of impaired T-lymphocyte functioning reflected in an impaired reaction to mitogens and allogenic lymphocytes (32). More recently, Wallace et al (42, 43) failed to find impairment of lymphocyte function in alveolar macrophages in cannabis smokers although they did find it in tobacco smokers.

The significance of these immunological impairments in chronic cannabis users is uncertain. There have been sporadic reports of ill health among chronic heavy cannabis users in Asia and Africa (32) but these reports are difficult to evaluate because of the confounding effects of poor living conditions and nutritional status (32). Three field studies of the effects of chronic cannabis use in Costa Rica (44), Greece (45), and Jamaica (46), failed to find any evidence of increased susceptibility to infectious diseases among chronic cannabis users. But less than 100 users were studied, a number which is too small to detect a small increase in the incidence of common infectious and bacterial diseases.

A recent study by Polen et al (47) compared health service utilisation by non-smokers and daily cannabis-only smokers enrolled in a health maintenance organisation. Their results provided suggestive evidence of an increased rate of treatment for respiratory conditions among cannabis-only smokers, although its significance is uncertain because infectious and non-infectious respiratory conditions were not separated. Further studies of this type may better assess how serious a risk chronic heavy cannabis smoking poses to the immune and respiratory systems (31).

5.6 Effects of cannabis on immunity in immunocompromised persons

Cannabis has been used by young adults in Western societies for over 30 years so the absence of epidemic infectious disease among these users makes it unlikely that cannabis smoking produces *major* impairments in the immune systems of users. The absence of such epidemics does not rule out the possibility that heavy cannabis use may impair immunity in ways that produce small increases in rates of common bacterial and viral illnesses (32). This could have escaped the notice of clinical observers.

Studies of the effects of cannabis use on patients with immune systems compromised by AIDS provide one way of detecting immunological effects of cannabis. If there were no effects in patients with compromised immune systems, it would be a reasonable to infer that there was little risk of immunological effects in recreational users.

A number of epidemiological studies of HIV positive homosexual men have examined the effects of cannabis and other drug use on progression to AIDS. Kaslow et al (48) studied progression to AIDS among 4,954 homosexual and bisexual men and found that HIV-positive cannabis users were *not* more likely to progress to AIDS and cannabis use was not related to immunological functioning. There was no relationship between cannabis use and progression to AIDS over six years in 451 HIV-positive men in the San Francisco Men's Health Study (49). The only study which found an association between cannabis and progression to AIDS was the Sydney AIDS Project in which 386 gay men were followed up over 12 months (50). This result may be at odds with the others because the study had a short follow up and many of the HIV positive cases may already have had AIDS (30).

A study of deaths in 64,855 HMO patients in California (51) did find an association between cannabis use and premature death from AIDS. Unmarried men had much higher rates of cannabis use than married men but in this study cannabis use was probably a marker for high-risk sexual behaviour rather than an independent risk factor.

5.7 Summary

Cannabis *smoke* is mutagenic (capable of inducing genetic mutation) and carcinogenic in animal tests and it contains many of the same carcinogens as tobacco smoke. It is therefore a potential cause of cancer in body cells that are chronically exposed to it, such as those of the aerodigestive and respiratory tracts.

There are case reports of aerodigestive tract cancers among relatively young adults who have been daily cannabis users. A case control study found an association between cannabis smoking and head and neck cancer but a large prospective study did not. The youth of the participants and the low rate of regular cannabis use in this prospective study reduced its ability to detect an increase in these cancers. Further follow-up and case control studies are needed to clarify the issue.

There is 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 but none of these was a planned study of the role of cannabis use in these cancers so replication of their results is required. There is no evidence that the rate of any of these cancers has increased over the past few decades.

In animals THC in high doses can impair cell-mediated and humoral immunity and reduce resistance to infection by bacteria and viruses. The relevance of these findings to human health is uncertain because the doses that produce these effects in animals are very high, and tolerance probably develops to the effects on the immune system in human users. The limited evidence on the immune effects of cannabis in humans is conflicting; the small number of studies that have produced adverse effects have not been replicated. The studies that have produced evidence of adverse effects have reported small changes that are within the normal range.

There has not been any increase in rates of infectious disease among chronic heavy cannabis users. Given the duration of large-scale cannabis use by young adults in Western societies, the absence of such epidemics makes it unlikely that cannabis smoking produces ***major*** impairments in the immune system. It is more difficult to exclude the possibility that chronic heavy cannabis use produces minor impairments in immunity.

There are three prospective studies of HIV-positive homosexual men two of which indicated that continued cannabis use did ***not*** increase rates of progression to AIDS and one of which suggested that it did. A recent epidemiological study which compared health service utilisation by nonsmokers and daily cannabis smokers provided suggestive evidence of an increased rate of medical care use for respiratory conditions among cannabis smokers. The most sensitive test of any small immunological effects of cannabis may come from studies of the therapeutic usefulness of cannabinoids in immunologically compromised patients, such as those undergoing cancer chemotherapy, or those with AIDS.

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6 The reproductive effects of cannabis use

Studies conducted in the mid-1970s showed that animals given large doses of cannabis or THC during pregnancy had lower levels of the gonadal hormones (testosterone and oestrogen) that control reproduction (1–5). There were also case reports of breast development in young men who had a history of heavy cannabis use (6). A study by Kolodny et al (7) found that chronic male cannabis users had lower levels of testosterone, a lower sperm count and motility, and more abnormal sperm than controls. These observations raised concerns that the use of cannabis by young adults during the 1970s and 1980s would impair fertility in men and adversely affect pregnancy outcomes in women. Cannabinoid receptors are expressed by cells in the hypothalamus and pituitary that regulate sex hormone production (8) so it is possible that THC can affect the functioning of the reproductive system.

6.1 Effects on the male reproductive system

Male animals given large doses of cannabis, crude cannabis extracts, THC and other cannabinoids showed lowered testosterone levels, retarded sperm maturation, reduced sperm count and sperm motility, and increased rates of abnormal sperm (1, 5, 9, 10). Although the mechanisms for these effects were uncertain, it was likely that they were a direct effect of THC on the testis, and an indirect effect on the hypothalamic hormones that stimulate the testis to produce testosterone (5).

Human studies of the effects of cannabis on male reproductive function produced mixed results (9). The study by Kolodny et al (7), which reported reduced testosterone, sperm production, and sperm motility and increased abnormalities in sperm, was not replicated in a larger, better controlled study of chronic cannabis users. This study failed to find any difference in testosterone level at study entry, or after three weeks of daily cannabis use (11). The significance of the animal findings for human cannabis users are uncertain (2) because testosterone levels in human cannabis users have generally been within the normal range (12).

6.2 Effects on the female reproductive system

In animal studies cannabis and THC interfere with the hormones controlled by the hypothalamic-pituitary-gonadal axis in non-pregnant female animals (1), delaying oestrous and ovulation (9). There have been very few human studies of the effects of cannabis on the female reproductive system because of fears that cannabis use may produce birth effects in women of childbearing age (13). An unpublished study by Bauman (1980 cited by Nahas (3)) compared the menstrual cycles of 26 cannabis smokers with those of 17 controls and found a higher rate of anovulatory cycles among the cannabis users. Mendelson and Mello (14) failed to find that cannabis use affected the female sex hormones, or the duration of the cycle. Mueller, Daling, Weiss and Moore (15) reported a modest association (OR = 1.7) between cannabis use and

infertility in a case-control study of 150 women with primary anovulatory infertility and 150 controls. The relationship was strongest in women who had used cannabis *less* frequently. In the absence of any other human evidence, Bloch (1), the Institute of Medicine (2) and Murphy (9) have argued that the animal evidence suggests that cannabis use probably inhibits human female reproductive function but it is uncertain how large these effects are.

6.3 Foetal development and birth defects

The possibility that cannabis use during pregnancy may adversely affect pregnancy outcomes is raised by evidence that THC crosses the placenta in animals (1) and humans (16). This makes it possible that THC, and other cannabinoids, may interfere with the development of the foetus, that is, may act as teratogens.

In mice, rats, rabbits, and hamsters large doses of cannabis or THC can produce foetal resorption, growth retardation, and malformations (1). Growth resorption and growth retardation have been more consistently reported than birth malformations (17) and the doses that produce malformations have been very high (17). Birth malformations have been observed more often after the administration of crude cannabis extract rather than pure THC, suggesting that other cannabinoids may produce any teratogenic effects. It is also unclear whether these teratogenic effects can be attributed to THC or to reduced food intake caused by the large doses of cannabis that have been used (1, 17). Bloch (1) concluded that THC was unlikely to be teratogenic in humans and was, at most, 'weakly teratogenic' in rodents and rats.

6.3.1 Human studies

Epidemiological studies of the effects of cannabis use on human reproduction have produced mixed results for a number of reasons. First, adverse reproductive outcomes and heavy cannabis use during pregnancy are relatively rare. This means that unless cannabis use produces a large increase in the risk of abnormalities, very large sample sizes will be required to detect adverse effects of cannabis use on foetal development. Many of the studies that have been conducted to date have been too small to detect effects of this size (18–20).

Second, societal disapproval of illicit drug use during pregnancy may discourage honest reporting when women are asked about drug use during their pregnancy (21). If a substantial proportion of cannabis users are misclassified as non-users, any relationship between cannabis use and adverse outcomes will be attenuated, requiring even larger samples to detect it (22).

Third, women who use cannabis during their pregnancies differ from those who do not in a variety of ways that may affect the outcome of their pregnancies. Cannabis users are, for example, more likely to smoke tobacco and use alcohol and illicit drugs during their pregnancy. They are also likely to have lower income, poorer education levels and poorer nutrition, all of which predict an increased risk of poorer pregnancy outcomes (10, 20, 23). These make it difficult to confidently attribute any poor birth outcomes to cannabis use rather than to other drug use, or to poor maternal nutrition and prenatal care.

Given these difficulties, there is reasonable consistency (although not unanimity) in the finding that cannabis use in pregnancy is associated with slightly reduced birth weight (24–26), and length at birth (23). This relationship has been found in the best-controlled studies, and it has persisted after statistically controlling for potential confounding variables (24, 25). A recent meta-analysis of these studies found that regular cannabis smoking during pregnancy possibly reduced birth weight but results varied considerably between studies (27). The mean weight reduction of 48 g (for any cannabis use vs no cannabis use during pregnancy) was much smaller than that associated with tobacco smoking during pregnancy, namely, 200 g (27).

The relationship between cannabis use and birth abnormalities is less certain. Milman (28) reported several cases of children with features similar to the Foetal Alcohol Syndrome (FAS) born to women who smoked cannabis during pregnancy but did not use alcohol. Epidemiological studies have largely not reported an increased rate of congenital abnormalities among children born to women who used cannabis during pregnancy (23, 25, 26, 29).

One study reported a five-fold increase in the rate of children with FAS-like features born to women who reported using cannabis (29). This finding was puzzling because there was *no* relationship between self-reported alcohol use and the 'foetal alcohol syndrome'. An additional study reported an increase in the crude rate of birth abnormalities among children born to women who reported using cannabis but this result was no longer statistically significant after adjustment for confounders (30). The study by Zuckerman et al is the most convincing study that failed to find an effect. A large sample of women was studied, among which a substantial proportion reported cannabis use that was verified by urinalysis. There was a low rate of birth abnormalities among the cannabis users, and no suggestion that their rate was higher than that in the controls.

6.4 Post-natal development

The most extensive research on the effects of cannabis use during pregnancy on the post-natal development of the child comes from the Ontario Prospective Prenatal Study (OPPS). This study assessed developmental and behavioural abnormalities in children born to women who reported using cannabis during pregnancy (31–39). A sample of 698 mothers were asked about their drug use during pregnancy and their children were measured on the Brazelton scales after birth and neurologically assessed at one month. In subsequent studies, these children were assessed using standardised scales at six and twelve months and throughout their childhood and into their adolescence (31).

The initial OPPS studies reported a developmental delay shortly after birth in the infants' visual system, and an increased rate of tremors and startle among the children born to cannabis users (31). The effects found at birth faded by one month, and there were no differences in performance on standardised tests of ability at six and twelve months. Small effects were again reported at 36 and 48 month follow ups (40) but these were not found at 60 and 72 months (41). These results are suggestive of a transient developmental impairment occurring among children who had experienced a shorter gestation and prematurity. It seems unlikely that the tests used in later follow-ups were

insensitive to the effects of prenatal cannabis exposure because they showed adverse effects of tobacco smoking during pregnancy on behavioural development at 60 and 72 months (40, 41).

The results of studies that ha attempted to replicate the OPPS findings have been mixed. Tennes et al (23) conducted a prospective study of the relationship between cannabis use during pregnancy and postnatal development in 756 women, a third of whom reported using cannabis during their pregnancy. The children were assessed shortly after birth using the same measures as Fried (20) and a subset were assessed at one year of age. There were no differences in behavioural development after birth between the children of women who did and did not use cannabis and there were no differences at one year. More recently, Day et al (42), have followed up children at age three born to 655 women who were asked about their substance use during pregnancy. They found a relationship between the mothers' cannabis use during pregnancy and the children's performances on memory and verbal scales of the Stanford-Binet Intelligence Scale at age three. A later follow up at age six did replicate the OPPS findings of increased impulsivity and impaired attention among children whose mothers had smoked cannabis during their pregnancy (43).

Fried and Smith (31) concluded after reviewing the literature that the effects of 'prenatal exposure to marihuana are subtle' and 'considerably moderated by other risk factors'. There were 'limited (if any) effects upon foetal growth and central nervous system functioning' and little evidence of effects on growth and behaviour during the toddler stage. They argued that there was suggestive evidence for subtle effects after the age of three in impulsivity, attention and problem solving, the significance of which needed to be clarified by further research.

A more sceptical view was expressed in a recent meta-analytic review of the effects on foetal development of maternal use of cocaine, a drug with a much greater reputation for foetal toxicity than cannabis (44). Frank et al concluded that, after controlling for exposure to tobacco and alcohol, there were no effects of prenatal cocaine use on physical of behavioural development to age six.

6.5 Summary

High doses of THC use disrupt the male and female reproductive systems in animals. THC interferes with hormones controlling reproduction, reducing testosterone secretion, sperm production, motility, and viability in males, and interfering with the ovulatory cycle in females. It is uncertain whether these effects occur in humans, given the high doses used in animal studies, the inconsistency of findings in studies of human males, and the fact that the effects observed in the positive human studies are still within the normal range.

Cannabis use during pregnancy probably leads to lower birthweight, although the decrease is much smaller than that produced by tobacco use. Cannabis use during pregnancy is unlikely to be a *major* cause of birth defects but it is possible that cannabis use during pregnancy produces a small increase in the risk of birth defects as a result of

exposure of the foetus in utero. There is suggestive evidence that infants whose mothers smoke cannabis during their pregnancy may experience behavioural and developmental effects during the first few months after birth and possibly in the longer term. These effects, if they exist, are likely to be smaller than comparable effects of alcohol use and tobacco smoking during pregnancy.

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7 Cardiovascular, respiratory and gastrointestinal effects

7.1 Cardiovascular effects of cannabis

One of the most consistent effects of cannabis in humans and animals is to increase heart rate (1–3). This change parallels the subjectively experienced 'high' and is related to the amount of THC in the blood (3, 4). Healthy young adults are only mildly stressed by these cardiovascular effects of cannabis (5).

An increased heart rate is most obvious in occasional cannabis users because regular users become tolerant to this and other effects of THC (4). Tolerance occurs within 24 hours in laboratory studies and even large amounts of cannabis may have little effect on heart rate (1, 2, 6–9). Tolerance to these effects has also been observed in field studies of chronic heavy cannabis users in Costa Rica (10), Greece (11), and Jamaica (12). These studies failed to find any adverse effects of cannabis on heart function.

7.1.1 Effects on patients with cardiovascular disease

Patients with ischaemic heart disease, hypertension, and cerebrovascular disease who use cannabis (13, 14) may experience cardiac arrhythmias, chest pain, and myocardial infarction (or heart attack). Because THC has analgesic effects it may mask chest pain, delaying treatment. Cannabis smoking also increases the level of carboxyhaemoglobin in the blood, decreases oxygen delivery to the heart and increases the work of the heart (4). Patients with cerebrovascular disease may experience strokes caused by changes in blood pressure and patients with hypertension may experience exacerbations of their disease for the same reason.

A number of laboratory studies have found that smoking cannabis cigarettes adversely affects patients with heart disease. Aronow and Cassidy (15) compared the effect of smoking a cannabis and a placebo cigarette on heart rate and the time required to induce chest pain in an exercise tolerance test. Heart rate increased by 43%, and the time taken to produce chest pain halved after smoking a cannabis cigarette. Aronow and Cassidy (16) compared the effects of smoking a single cannabis cigarette and a high nicotine cigarette in 10 men with heart disease, all of whom were cigarette smokers. Smoking cannabis produced a 42% increase in heart rate, compared with a 21% increase after smoking the tobacco cigarette. Exercise tolerance time was halved after smoking a cannabis cigarette by comparison with a tobacco cigarette. These findings have been confirmed by Gottschalk and colleagues (17).

7.1.2 Significance of cardiovascular effects

It seems unlikely that healthy young adults who occasionally smoke cannabis develop heart disease as a result of their cannabis smoking. Most of these cannabis users discontinue their use by their late 20s (18, 19). A recent study (20) provides support for predictions that adverse cardiovascular effects may occur in a minority of chronic

cannabis users who continue to use cannabis into their late 40s and early 50s, the age of highest risk for heart disease (21).

Mittleman et al reported a case-crossover study of the possible role that smoking cannabis may play in triggering an acute myocardial infarction (heart attack) (20). They asked 3882 patients who had had a myocardial infarction in the previous 4 days about their use of marijuana in the hour before it occurred, and compared this with their typical frequency of use. Only 3.5% of all patients, and 12.5% of those under the age of 44 years, had smoked cannabis in the previous year but it increased the risk of a myocardial infarction 4.8 times in the hour after use. The risk dropped rapidly after the first hour, as expected from the effects that THC and carbon monoxide from smoking have on heart function. The effect of smoking cannabis was smaller than the effect of cocaine use observed in earlier studies (a 24 fold increase). Mitteleman et al estimated that a 44-year-old adult who used cannabis daily would increase their annual risk of an acute cardiovascular event by 1.5% to 3%. They concluded that: 'smoking marijuana is a rare trigger of acute myocardial infarction' that 'may pose a health risks to patients with coronary heart disease and perhaps to individuals with multiple coronary risk factors' (p. 2808). The significance of this contribution may rise as the proportion of older adults who smoke cannabis increases.

7.2 Effects on the respiratory system

It is likely that regular cannabis smoking adversely affects the respiratory system (22). Cannabis smoke is similar to tobacco smoke, and contains a higher proportion of particulate matter and more of some carcinogens (e.g. benzpyrene) than tobacco smoke (22, 23). The inhalation of cannabis smoke therefore deposits carcinogenic substances on lung surfaces. Cigarette smoking is a cause of bronchitis, emphysema, and cancers of the lung, oral cavity, trachea, and oesophagus (24). Although tobacco smokers smoke many more cigarettes than cannabis smokers, cannabis smokers typically inhale more deeply, and hold their breath for longer, thereby depositing more particulate matter in the lung (22).

7.2.1 Chronic bronchitis and obstructive pulmonary disease

Convincing evidence that chronic cannabis use may impair lung function and cause symptoms of respiratory disease comes from a series of studies conducted by Tashkin and his colleagues since the mid 1970s (22). One of their early studies evaluated the effects of heavy daily cannabis smoking on respiratory function. The subjects were young male cannabis smokers who were studied in a closed hospital ward where they were allowed free access to cannabis for 47 to 59 days. There was a significant decrease in the function of large and medium-sized airways during the study and the degree of impairment was related to the number of cannabis cigarettes smoked, suggesting that the quantity of inhaled irritants was the important factor.

Tashkin and his colleagues (25) subsequently studied cannabis only smokers (MS, n = 144), cannabis and tobacco smokers (MTS, n = 135), tobacco only smokers (TS, n = 70), and non-smoking controls (NS, n = 97). These subjects were followed to study changes in lung function, signs and symptoms of respiratory disease, and histopathological changes that precede the development of cancer.

At baseline Tashkin et al (25) found more symptoms of bronchitis (such as cough, bronchitic sputum production, wheeze and shortness of breath) in all types of smokers (MS, MTS, TS) than non-smokers. Cannabis and tobacco smokers did not differ in the rates of these symptoms. Lung function tests showed poorer functioning and greater abnormalities in small airways among tobacco smokers whereas cannabis smokers had poorer large airways function than non-cannabis smokers.

Follow up studies of this conort have shown different effects of cannabis and tobacco smoking on lung function (26). The first follow up study two to three years after the baseline study retested almost half of these subjects, most of whom were in the same smoking categories as at baseline. At both baseline and follow up, cough, sputum, and wheeze were more common in smokers than among nonsmokers. There was no significant change in the respiratory status of any of the smoking groups over time when those individuals who ceased smoking were excluded. The same was found when the subjects were followed up 3 to 4 years after first assessment. In addition, the group that smoked both cannabis and tobacco showed both types of damage found in those who only smoked cannabis or tobacco.

Tashkin and colleagues (27, 28) studied the histopathology of the lungs in a sample of their cohort. Fligiel et al (27) compared the bronchial morphology of 30 males who were heavy smokers of cannabis-only with those of 17 cannabis and tobacco smokers 15 tobacco only smokers and 11 nonsmoking controls. All subjects who smoked had more severe abnormalities than nonsmokers. Many of these were more common in cannabis smokers, and they were most marked in men who smoked cannabis and tobacco. These abnormalities occurred at a younger age in cannabis than tobacco smokers, despite the fact that the cannabis smokers smoked less than a quarter as many 'joints' as the tobacco smokers smoked cigarettes.

Additional research (29, 30) suggests a number of reasons why cannabis smoking may be more toxic to the respiratory system than tobacco smoking. Laboratory studies show that cannabis smokers inhale a larger volume of smoke than tobacco smokers (40% to 54% more). They also inhaled more deeply and held their breath about four to five times longer than tobacco smokers. As a result, they retained more particulate matter, and absorbed three times more carbon monoxide, than tobacco smokers (29).

Other studies have replicated some of the findings of Tashkin and colleagues. Bloom et al (31) examined the relationship between smoking 'nontobacco' cigarettes and respiratory symptoms and respiratory function in the general population. Their sample comprised 990 individuals aged under 40 years who were followed up in a prospective community study of obstructive airways disease. The proportion who said that they had ever smoked a 'non-tobacco' cigarette was 14% (the same as the rate of cannabis smoking in general population surveys at the time), 9% were current and 5% ex-smokers of 'non-tobacco' cigarettes. On average non-tobacco cigarettes were smoked 7 times per week for 9 years. Non-tobacco smokers were more likely to have smoked tobacco and they inhaled more deeply than tobacco only smokers.

Non-tobacco smokers reported more cough, phlegm, and wheeze, regardless of whether they smoked tobacco or not. They also had poorer respiratory function. Those who had never smoked had the best functioning, followed in order of decreasing function by

current cigarette smokers, current non-tobacco smokers, and current smokers of tobacco and non-tobacco cigarettes. Non-tobacco smoking alone had a bigger effect on respiratory function than tobacco smoking alone, and the effects of both types of smoking on respiratory function was additive.

Sherril et al (32) have reported follow up data on respiratory symptoms and respiratory function in this sample. Rates of non-tobacco use declined over time, as did the quantity of cannabis that was smoked per week. At each follow-up non-tobacco smokers were twice as likely to report chronic cough, chronic phlegm and wheeze than non-smokers. The rate of reported symptoms increased with the number of non-tobacco cigarettes smoked per week and with the length of time that non-tobacco cigarettes were smoked. Non-tobacco smokers showed impairment on all indices of respiratory function.

Taylor et al (33) studied symptoms of respiratory disease and respiratory function in 1037 young New Zealand adults who were followed from birth until age 21. They compared symptoms of respiratory disease and respiratory function in those who were: cannabis dependent, cigarette smokers and non-smokers of tobacco and cannabis. Tobacco smokers had a higher rate of chronic bronchitis, wheeze and cough than non-tobacco smokers and the rate of these symptoms increased with the number of cigarettes smoked per day. Cannabis dependent subjects had higher rates of wheezing, shortness of breath, chest tightness and morning sputum production than non-smokers, after taking account of tobacco use. Among cannabis dependent subjects the effects in cannabis users were similar to those in tobacco smokers of 1–10 cigarettes/day. A higher proportion of cannabis dependent subjects had impaired respiratory function and the adverse effects of tobacco and cannabis smoking on respiratory function were additive.

7.2.2 Respiratory cancers

As discussed in detail in Chapter 5, there is evidence that cannabis *smoke* is mutagenic and carcinogenic and a potential cause of cancer in body cells that are regularly exposed to it, such as those of the aerodigestive and respiratory tracts. There are case reports of aerodigestive tract cancers among relatively young adults who have been daily cannabis users. A case control study has found an association between cannabis smoking and head and neck cancer (34). The only prospective cohort study to date has not found evidence of increased incidence of head and neck or respiratory cancers, although it found evidence of increased rates of prostate cancer. The relative youth of the participants and the low prevalence of regular cannabis use in the latter study reduced its ability to detect an increase in respiratory cancers. There is also evidence that the lungs of chronic cannabis smokers show changes in gene expression that appear to be precursors of cancer in tobacco smokers (35). Further follow ups of the Sidney et al cohort (36), and additional case control studies, are needed to clarify the issue (see Chapter 5).

7.3 Effects on the gastrointestinal system

Studies in experimental animals have not found any evidence that THC causes liver damage (37–39). Liver weight was reduced but this may have been caused by reduced food consumption because very high doses of THC were used. There is no human evidence that the chronic use of cannabis disturbs liver function (4).

Anecdotal evidence suggests that cannabis increases appetite ('the munchies' or 'hash hungries') (40–42). Cannabinoids reduce food and water intake in animals (4) but experimental studies in humans provide some support for the anecdotal reports (43–45). THC in the synthetic form of dronabinol (Marinol) has been shown to produce weight gain when used to treat nausea and vomiting caused by cancer chemotherapy. A similar weight gain was reported when used in patients with HIV infection. There are now objective data to support these anecdotal reports, and these suggest that THC has a potential therapeutic use as an appetite stimulant.

7.4 Summary

Smoking cannabis increases heart rate and affects blood pressure but there is no evidence that these effects have a permanently deleterious effect on the normal cardiovascular system. These effects are less benign in patients with hypertension, cerebrovascular disease and coronary atherosclerosis in whom THC may increase the work of the heart. The seriousness of these effects in persons with cardiovascular disease will be determined as persons who initiated cannabis use in the late 1960s enter the risk period for cardiovascular disease.

Cannabis smoking causes chronic bronchitis and impairs functioning of the large airways and produces pathological changes in lung tissues that may be precursors of lung cancer. Case studies and a case-control study suggest that cannabis may cause cancers of the aerodigestive tract. Additional studies of these cancers are a high priority.

There appears to be little or no human or animal evidence that cannabinoids affect liver function. The most interesting gastrointestinal effect of cannabis is its therapeutic use in reducing nausea and stimulating appetite in cancer and AIDS patients.

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8 Effects on motivation and the risk of dependence

8.1 Motivational effects

Chronic daily cannabis use has been reported to impair motivation in users in Egypt and the Caribbean (1). Young cannabis users in the USA in the early 1970s who were apathetic, withdrawn, lethargic and unmotivated (2, 3) were said to suffer from an 'amotivational syndrome' (3, 4). It is difficult in these cases to disentangle the effects of chronic cannabis use from those of poverty, poor education and pre-existing psychiatric disorders (5–7).

The effects of cannabis use on motivation were assessed in a number of field studies of chronic cannabis users in Costa Rica (8), Jamaica (9) and the USA (10). Rubin and Comitas (9), for example, found that Jamaican farmers who regularly smoked cannabis worked harder but less efficiently after using cannabis. A study of Costa Rican cannabis smokers produced mixed evidence on the effect of chronic cannabis use on job performance. Carter et al (8) compared 41 heavy cannabis users (10 cannabis cigarettes per day for ten or more years) with 41 nonusers of cannabis matched on age, marital status, education, occupation, and alcohol and tobacco use. The nonusers were more likely: to have a stable employment history, to have been promoted and given pay rises, and to be in full-time employment. Users spent more of their incomes on cannabis and were more likely to be in debt. Among users, however, those who had steady jobs or who were self-employed smoked twice as many cannabis cigarettes per day as those with more frequent job changes, or those who were chronically unemployed.

A follow up study of long-term cannabis users in the USA suggests that the amotivational syndrome is rare among long-term cannabis users. Halikas et al (10) assessed symptoms of the amotivational syndrome in 100 regular cannabis users six to eight years after they were first studied. Only three individuals had ever experienced amotivational symptoms in the absence of depression and their use did not differ from that of other cannabis users.

Laboratory studies of long-term heavy cannabis use have also failed to clearly show that cannabis impairs motivation (5). Early studies conducted by the LaGuardia Commission (11) reported deterioration in behaviour among prisoners given daily doses of cannabis over a period of some weeks but these reports were based upon uncontrolled observation. A study using standardised measures of performance failed to observe such effects (11). In this study 10 casual and 10 heavy cannabis smokers were observed in a laboratory over a 31-day study period. For 21 of these days subjects were given access to as many cannabis cigarettes as they earned by performing a simple task. All subjects earned the maximum number of points allowed per day throughout the study and their output was not affected by cannabis use. Providing similar access to alcohol in heavy drinking subjects in the same setting profoundly disrupted performance. Similar results were reported in a study by Campbell (12) in which young cannabis users were given

high doses of cannabis. They showed no gross behavioural changes, no social deterioration, and no alterations in intellectual functioning but their productivity was reduced when they were given 30 mg of THC per day, a dose that many subjects found unpleasant.

Schwenk (13) has recently reviewed evidence on the relationship between cannabis use and job performance in laboratory studies, surveys, observational studies, anthropological studies and studies of drug testing. He concluded that the associations between cannabis use and poor job performance in laboratory studies and surveys were small. Schwenk argued that these results were more consistent with the hypothesis that there was a relationship between the characteristics of cannabis users and poor job performance rather than with the hypothesis that cannabis use was a cause of poor job performance.

The amotivational syndrome remains contentious because of differences of opinion about the value of clinical observations and controlled studies. Those who accept the existence of the syndrome appeal to the small number of cases fitting the description of an 'amotivational syndrome' (14). Sceptics are more impressed by the unsupportive field and laboratory studies. If there is an amotivational syndrome, it is a relatively uncommon consequence of prolonged heavy cannabis use. Research suggests that the features of the 'amotivational syndrome' can be better explained as symptoms of chronic cannabis intoxication in cannabis dependent users, thereby obviating the need to invent a new psychiatric syndrome (5).

8.2 Is there a cannabis dependence syndrome?

For much of the 1960s and 1970s cannabis was not regarded as a drug of dependence because it did not seem to produce tolerance or a withdrawal syndrome like that seen in alcohol and opioid dependence. Views changed in the late 1970s and early 1980s with the adoption of a broader conception of drug dependence (15). This new conception reduced the emphasis on tolerance and withdrawal and placed more emphasis on the compulsion to use, a narrowing of the drug using repertoire, rapid reinstatement of dependence after abstinence, and the high salience of drug use in the user's life. It was reflected in the Third and Fourth Revised Editions of the Diagnostic and Statistical Manual (DSM-III-R and DSM-IV) of the American Psychiatric Association (16, 17).

8.2.1 Drug dependence in DSM-IV

'The essential feature of Substance Dependence is a cluster of cognitive, behavioral and physiologic symptoms indicating that the individual continues use of the substance despite significant substance-related problems' (p.176) (16). A diagnosis of Substance Dependence is made if *three or more* of the following criteria occur at any time in the same 12-month period:

'1. tolerance, as defined by either of the following:

   a. need for markedly increased amounts of the substance to achieve intoxication or desired effect

   b. markedly diminished effect with continued use of the same amount of the substance

2. withdrawal, as manifested by either of the following:
   a. the characteristic withdrawal syndrome for the substance
   b. the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. the substance is often taken in larger amounts or over a longer period than was intended;
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use;
5. a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors, driving long distances), use the substance (e.g. chain smoking), or recover from its effects;
6. important social, occupational, or recreational activities are given up or reduced because of substance use;
7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.' (16).

8.2.1 Cannabis tolerance and withdrawal: experimental evidence

Cannabis users can develop tolerance to the effects of THC and they can experience withdrawal symptoms under certain conditions. Tolerance to many of the behavioural and physiological effects of THC has been demonstrated in humans and animals (18–23). The precise mechanisms are unknown but they probably involve changes in cannabinoid receptor function (20, 24).

Jones and Benowitz (25) studied the effects of 210 mg dose of oral THC per day given in a fixed dosing schedule to healthy male volunteers with extensive histories of cannabis use. Over the 30-day study, the positive effects of intoxication declined and there was a recovery in social, cognitive and psychomotor performance. Georgotas and Zeidenberg (19) also reported tolerance to the subjective effects of cannabis in humans.

Early case reports of cannabis withdrawal symptoms in humans have been supported by abstinence symptoms in laboratory studies (18, 21, 26). Studies in clinical and non-clinical samples of long-term cannabis users have reported withdrawal symptoms, such as anxiety, insomnia, appetite disturbance and depression (27–30).

Jones and Benowitz (25) abruptly withdrew regular cannabis users after two weeks on high doses of oral THC. Within six hours, they complained of 'inner unrest' and after 12 hours they reported 'irritability, insomnia, and restlessness' that were also observed by staff. These symptoms were correlated with THC dose and frequency of use, and were reduced after using cannabis (22). Georgotas and Zeidenberg (19) reported similar symptoms during the first week of abstinence in subjects who had received 210 mg of smoked cannabis a day for four weeks. Recent laboratory studies by Haney et al (31, 32) have reported withdrawal symptoms at much lower doses of THC given orally and by smoking. The most common symptoms were anxiety, depression and irritability.

Kouri and Pope (33) reported a controlled prospective study of withdrawal symptoms among chronic cannabis users who were assessed daily on various withdrawal symptoms while in a hospital ward for 28 days. Their ratings of mood, anxiety, depression and irritability were compared to those of two control groups of abstinent former heavy cannabis users and non-users of cannabis. During the course of the 28 days the chronic cannabis users showed decreases in mood and appetite and increases in irritability, anxiety, physical tension, and physical symptoms, and their scores on the Hamilton Depression and Anxiety scales increased. These appeared within 24 hours and were most marked in the first 10 days although the increase in irritability and physical tension persisted throughout the 28-day observation period.

Research using the cannabinoid antagonist SR 141716A (which immediately reverses the effects of THC) has shown that a withdrawal syndrome can be produced in rats, mice and dogs that have been maintained on THC (34, 35). The antagonist produces compressed and accentuated symptoms that are much more dramatic than the milder and more prolonged symptoms that occur under usual conditions of human use (36). The relatively long half-life and complex metabolism of cannabis may also result in a less intense withdrawal syndrome than drugs such as opiates (24).

8.2.2 Epidemiological studies of cannabis dependence

The Epidemiological Catchment Area (ECA) study estimated the rates of cannabis abuse and dependence in US population in the early 1980s (37). It found that 4.4% of the US population had a diagnosis of cannabis abuse or dependence according to DSM-III criteria. A third of those with lifetime cannabis abuse or dependence (38%) reported problems with cannabis use in the last year. Men had a higher risk of cannabis dependence than women, with the highest risk among 18 to 29 year olds. (38).

The most common symptoms reported by those who were cannabis dependent were: requiring larger amounts (21%), having psychological (21%) or social (17%) problems attributed to cannabis, and inability to reduce use (8%). Few reported health problems (5%) or withdrawal sickness (3%) (39). Surveys using similar methods to the ECA have produced similar estimates of the rate of cannabis dependence in Canada and New Zealand (40–42).

The National Comorbidity Survey (NCS) conducted in the USA between 1990 and 1992 (43) found that 4.2% of adults met DSM-III-R criteria for cannabis dependence at some time in their lives. The proportion of people who had ever used cannabis who met criteria for cannabis dependence was 9%. This compared to 32% of nicotine, 23% of heroin, 17% of cocaine, 15% of alcohol and 11% of stimulant users who met criteria for dependence.

The Australian National Survey of Mental Health and Well-being (44) found that 1.7% of Australian adults met the International Classification of Diseases (ICD-10) (45) criteria for a diagnosis of cannabis dependence, and 0.1% met criteria for harmful use in the previous year. One in four (23%) of those who had used cannabis more than five times in the last year met criteria for cannabis dependence or harmful use.

8.2.3 Studies of long-term cannabis users

Studies of long-term cannabis users in Egypt (46), India (47), Germany (2), Greece (48), Costa Rica (8) and Jamaica (9) did not study symptoms of dependence other than withdrawal, which then defined dependence. Stereotyped use patterns, persistent desire to quit, tolerance, chronic intoxication, mild withdrawal and continued use despite problems were reported in the Egyptian, Indian and Jamaican studies but there were no withdrawal symptoms reported in the Costa Rican, Jamaican or Greek studies.

Kandel and Davies (49) described problems reported by a subset of daily cannabis users (aged 28–29 years) who were recruited in a large prospective study of 1,222 adolescents. The major adverse consequences of cannabis use reported were: cognitive deficits, reduced energy, depression, and, among males, problems with their spouse.

Recent Australian surveys of long-term cannabis users diagnosed a substantial proportion as cannabis dependent. Among 243 rural cannabis users, who had used cannabis several times a week for 19 years, 57% qualified for lifetime DSM-III-R and ICD-10 cannabis dependence diagnoses (30). The most common symptoms reported were: frequent intoxication during daily activities (73%) and a strong urge to use cannabis (75%). Few reported withdrawal symptoms (5%) or using cannabis to relieve withdrawal symptoms (20%), although 54% reported tolerance. Only 26% believed they had a problem with cannabis and only 9% had sought help to cut down or stop.

Among 200 young Sydney adults who had used cannabis at least weekly for 11 years, 92% met criteria for a DSM-III-R lifetime diagnosis of dependence and 40% were classified as severely dependent (29). Tolerance and withdrawal were reported by 78% and 76% respectively and use to relieve withdrawal symptoms by 39%. Most met criteria for cannabis dependence in the past year according to DSM-III-R (77%) and ICD-10 (72%) criteria. A follow-up of these users found that cannabis use and dependence symptoms were stable over a year (50). The majority (81%) of the follow-up sample met criteria for a dependence diagnosis during the last year on three measures of dependence.

8.2.4 Clinical populations

Cannabis dependent persons seek help with cannabis-related problems in Australia, the United States and Europe. The National Census of Clients of Australian Treatment Service Agencies (51, 52) found that the proportion of cases in whom cannabis was the *main* drug problem increased from 4% in 1990 to 7% in 1995. Between 1994 and 1998 cannabis was the primary drug of abuse for between 11% and 26% of clients of treatment agencies in the United States (53, 54). Cannabis was the primary drug problem for between 2% and 16% of clients attending treatment agencies in the European Union in 1998 (55).

A Swedish treatment program (56) reported that its clients typically complained of: unsuccessful attempts to stop or moderate use and frequent (often daily) intoxication, despite suffering adverse effects connected with their cannabis use. These included sleeplessness, depression, impaired concentration and memory, and blunting of emotions.

Stephens and colleagues (57) described the symptoms reported by 382 persons who sought help to cease cannabis use. These included: an inability to stop using (93%), feeling bad about using cannabis (87%), procrastinating (86%), loss of self-confidence (76%), memory loss (67%) and withdrawal symptoms (51%). Similar experiences have been reported among users in recent US (28, 58) and Australian studies of interventions for problem cannabis use (27). In the Australian study, among 180 long-term cannabis users seeking help, the most common symptoms were withdrawal and use to relieve withdrawal.

8.2.5 The risk of cannabis dependence

People who use cannabis daily over weeks to months are most likely to become dependent. Kandel and Davis (49) estimated that one in three daily cannabis users met DSM-III criteria for dependence. The risk of dependence among less frequent users of cannabis is lower (59). In the ECA study, 17% of those who used cannabis more than 5 times met DSM-III criteria for dependence at sometime in their lives (38). In the National Comorbidity Study (NCS), Anthony et al (43) estimated that the proportion of persons who had ever used alcohol, amphetamines, cannabis, cocaine, heroin, nicotine and sedatives who met DSM-III-R criteria for dependence on each drug at some time in their lives were: 32% for nicotine, 23% for heroin, 15% for alcohol and cocaine and 9% for cannabis.

These estimates suggest the following rules of thumb about the risks of cannabis dependence. For those who have ever used cannabis the risks of developing dependence is probably of the order of one chance in ten. Among those who use the drug more than a few times the risk of developing dependence is in the range of from one in five to one in three. As a rule, the more often cannabis has been used, and the longer it has been used, the higher the risk of dependence.

The following factors also predict a higher risk of regular involvement with cannabis: poor academic achievement, deviant behaviour in childhood and adolescence, nonconformity and rebelliousness, personal distress and maladjustment, poor parental relationships, earlier use, and a parental history of drug and alcohol problems (49, 60–62).

8.2.6 The consequences of cannabis dependence

The large gap between the ECA estimates of cannabis abuse and dependence in the community and the number of cannabis users who seek treatment suggests that many of these cases remit without treatment, as is true of alcohol abuse and dependence (63). Kandel and Davies (49) found that by age 28 to 29, less than 15% of daily cannabis users were still using daily, and Bachman et al have found that most regular cannabis users discontinued their use during the mid to late twenties (64).

Among the minority of regular cannabis users who are sufficiently troubled to seek help the major complaints are: a loss of control over their cannabis use, cognitive and motivational impairments which may interfere with work performance, lowered self-esteem and depression, and complaints by spouses and partners about their frequent

intoxication (see above). There is no doubt that some dependent cannabis users report impaired performance and a reduced quality of everyday life but more research is necessary to decide how common this is, and how impaired cannabis dependent persons are.

8.2.7 The treatment of cannabis dependence

Little research has been done on the sort of assistance that should be given to cannabis users who seek help to stop using cannabis (65). Although many users may succeed in quitting without professional help we need to assist those who are unable to stop on their own. It is not clear what type of treatment should be provided for dependent cannabis users who have repeatedly failed to stop using cannabis and seek help.

Roffman et al (66) reported one of the few randomised controlled trials comparing group based relapse prevention and social support. Subjects were 120 men and women (aged 32 with 16 years of cannabis use) who answered advertisements for help to stop using cannabis. One-month after treatment only 30% of their patients were still abstinent and by the end of a year only 17% were abstinent.

Stephens et al (67) recently reported another study of behavioural treatment for cannabis dependence in 291 subjects. Subjects were randomly assigned to one of three treatments: (1) a 14 session group based relapse prevention intervention (RPSG) similar to their earlier study but with more sessions; (2) an individualised advice (IAI) two session intervention using principles of motivational interviewing adapted from Miller's Drinker's Check-up; and (3) a delayed treatment condition (DTC) in which participants did not receive any treatment for four months.

At the four month follow up all three groups had reduced their cannabis use but the two treatment groups showed the largest reduction and did not differ from each another. In the treatment groups 37% were abstinent compared with only 9% in the delayed treatment group. The amount of cannabis use also declined by 70% in the treatment groups and by 30% in the delayed treatment groups. Abstinence rates declined over time but the two treatments did not differ at 7, 13 and 16 months after treatment. Twenty-two percent of participants were abstinent throughout the 16 month study and their abstinence was corroborated by partners and family members.

Budney, Higgins, Radinovich and Novy (68) reported a controlled comparison of three treatments for 60 cannabis dependent patients. They compared three treatments: motivational enhancement to quit (M), motivational enhancement plus behavioural coping skills (MBT), and MBT plus incentives to remain abstinent (MBTV). In the latter, vouchers for retail items were exchanged for urine samples that were negative for cannabinoids. The MBTV group had a longer period of continuous abstinence than the other two groups which did not differ from each other. By 14 weeks post-treatment fewer than 10% of participants had been continuously abstinent from cannabis.

Copeland, Swift, Roffman and Stephens (69) replicated the study by Stephens et al (67) in an Australian sample. They randomly assigned 229 cannabis dependent adults to three treatments: a six session cognitive behavioural intervention; a single session cognitive

behavioural treatment, and a delayed treatment control group who were offered treatment four months after the other two groups. Only 6.5% of all subjects (n = 11) were continuously abstinent during the 8-month follow up period and all of these were in the treatment groups. There were greater reductions in cannabis related problems and in dependence symptoms in the two treatment groups.

So far rates of continuous abstinence from cannabis have been low in the treatments tested, although there have been substantial reductions in rates of use and problems related to use. Nonetheless, much more research is needed before sensible advice can be given about the best ways to achieve abstinence from cannabis. In the absence of better evidence of treatment effectiveness, people offering treatment for cannabis dependence should avoid replicating experience in the treatment of alcohol dependence where inpatient treatment has been widely adopted in the absence of any evidence that it is more effective than outpatient forms of treatment (70, 71).

8.3 Summary

There is no compelling evidence for an amotivational syndrome among chronic cannabis users. Some heavy users do complain of impaired motivation but this pattern of behaviour is better explained as a symptom of chronic intoxication among persons who are cannabis dependent.

There is good evidence that a cannabis dependence syndrome can develop in some chronic cannabis users. These users develop tolerance, experience withdrawal symptoms on cessation of use, have problems controlling their cannabis use, and continue to use despite the experience of adverse personal consequences of use. Cannabis dependence is the most common form of drug dependence after alcohol and tobacco in the USA and Australia. 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. Few cannabis dependent persons seek treatment, probably because many disorders remit without treatment. It is not clear as yet what advice should be given to the minority of dependent cannabis users who seek help to stop their use.

8.4 References

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9 The effects of cannabis use on cognitive functioning

Cannabis acutely impairs cognitive performance, so there is an understandable concern that its chronic use may cause longer lasting impairment of cognitive functioning. This possibility seemed to be supported by clinical observers in the USA during the early 1970s (e.g. Kolansky and Moore, (1, 2)) who reported that young adults who had used cannabis weekly or more often had 'poor attention span, poor concentration, confusion' (2). More recently, some long-term cannabis users seeking help to stop using cannabis have complained that their memory and thinking is impaired (3). The difficulty with these reports has been in ruling out alternative explanations, namely, that cognitive impairment preceded cannabis use or was the result of other drug use.

9.1 Cross-cultural studies

One research strategy has been to examine cognitive performance in heavy cannabis users in cultures with a tradition of heavy use. An early report by Soueif (4) illustrates the problems with this strategy. Soueif studied Egyptian male prisoners of whom 850 were hashish smokers and 839 controls. The hashish users performed more poorly than the controls on ten of sixteen measures of perceptual speed and accuracy, distance and time estimation, immediate memory, reaction time and visual-motor abilities (4–7). The findings were weakened because the two groups also differed in ways that may have affected cognitive performance, namely, the hashish users were less well educated and more likely to use opiates and alcohol (8).

In the late 1960s the National Institute on Drug Abuse (NIDA) commissioned three cross-cultural studies in Jamaica, Greece and Costa Rica to assess the effects of chronic cannabis use on cognitive functioning (among other things). It was assumed that any cognitive effects of chronic daily cannabis use should be apparent in users with a long-history of heavy cannabis use, a pattern of use that was common in these cultures.

Bowman and Pihl (9) reported two field studies of cannabis users in Jamaica who had been daily cannabis users for a minimum of 10 years (23 joints per day) while controls had no experience with cannabis. No differences were found between the users and nonusers in either study or when rural and urban samples were combined. Rubin and Comitas (10) reported similar findings in a study of 30 Jamaican cannabis users who had used for 17.5 years and 30 nonusers.

The Greek study (11, 12) compared 47 daily hashish users (who used for 23 years) with 40 controls matched for age, sex, education, demographic region, socioeconomic status and alcohol consumption. The groups did not differ in total IQ score on either the WAIS or Raven's Progressive Matrices but the controls obtained a higher verbal IQ score than hashish users and the users performed worse than controls on all but one of the subtests of the WAIS (13). Since subjects did not abstain from hashish before testing, it was not clear whether these differences were due to long-term hashish use, or the acute effects of the drug at the time of testing.

In the Costa Rican study (14), researchers compared 41 males who had used 10 cannabis joints per day for 17 years with matched controls on a test battery that assessed neuropsychological, intellectual and personality variables. The Costa Rican users did not differ significantly from controls on any test. Page, Fletcher and True (15) followed up this sample after 10 years, by which time they had used cannabis for around 30 years. No differences were detected on any of the original tests but there were significant differences on three new tests of sustained attention and short-term memory. They emphasised that these differences were 'quite subtle' and 'subclinical', with only a small number of subjects clinically impaired. It was also difficult to exclude the possibility that the differences were due to recent cannabis use, since 24 hour abstinence was requested but not verified.

A number of studies of long term Indian cannabis users have also reported cognitive impairment. Agarwal et al (16) studied forty subjects who had used bhang daily for about 5 years. A comparison of their scores with normative data found that 18% had memory impairment, 28% showed mild intellectual impairment (IQs less than 90), and 20% showed substantial cognitive disturbances on the Bender-Gestalt Visuo-Motor Test. Wig and Varma (17) substantially replicated these results and Mendhiratta, Wig and Verma's (18) found that 50 heavy cannabis users reacted more slowly and had poorer concentration and time estimation than 50 matched controls.

The cross-cultural studies of long-term heavy cannabis users provide equivocal evidence of cognitive impairment among long-term cannabis users. They have either failed to find any differences or have found modest cognitive impairment in persons with a long history of heavy cannabis use. Their negative results cannot be attributed to short duration or low intensity of cannabis use because these subjects had used cannabis for between 17 and 23 years, and the amount of THC consumed per day ranged from 20–90 mg in the Jamaican study to 120–200 mg in the Greek sample. The differences that were observed are difficult to interpret because users often had higher rates of polydrug use, poorer nutrition, poorer medical care, and higher rates of illiteracy than controls, all factors which may have biased these studies towards finding poorer performance among cannabis users. Many of these studies also failed to ensure that subjects were not intoxicated by cannabis at the time of testing.

9.2 Studies of Western cannabis users

Studies of the cognitive performance of North American cannabis users have generally been on college students with much shorter histories of cannabis use than the chronic users in the cross-cultural studies (19). It is therefore unsurprising that most of these studies have failed to find evidence of cognitive impairment in cannabis users (19). One study to which these criticisms do not apply is that of Schaeffer et al (20) who studied cognitive impairment in 10 heavy cannabis users in the United States who used cannabis daily for religious reasons. All were Caucasian and all had been born and educated in the USA. All had smoked between 30 and 60 gms of cannabis a day for over 7 years and they had *not* used alcohol or any other psychoactive substances. At the time of testing, all subjects had evidence of recent heavy cannabis use in their urine. Overall, their scores on the WAIS IQ test were in the superior to very superior range, and their scores on all other tests were within normal limits but with only 10 subjects the study had a limited capacity to detect cognitive impairment.

9.3 Laboratory studies of daily cannabis use

Another strategy for investigating the cognitive effects of chronic cannabis use has been to study the cognitive performance of persons who use cannabis daily over periods of weeks. These studies have controlled the quantity, frequency, and duration of cannabis use, as well as nutrition and other drug use, by observing subjects in a hospital ward while they use cannabis. All such studies have used pre- and post-drug observation periods. The sample sizes in these studies have been small and cannabis has been used from 21 to 64 days.

Dornbush et al (21) administered cannabis containing 14 mg THC to 5 regular cannabis users for 21 days. They were tested before and 60 minutes after using cannabis on short-term memory and digit symbol substitution. Performance on the short-term memory test decreased on the first day of drug administration but gradually improved until by the last day of the study it had returned to baseline. Performance on the digit symbol substitution test was unaffected by cannabis but improved with time as a result of practice.

Mendelson, Rossi and Meyer (22) studied the effects of 21 days of cannabis use on 20 healthy, young male subjects who smoked as much cannabis as they wanted to. Short-term memory was impaired during intoxication but there was no impairment of performance before or after cannabis smoking. Similar failures to detect cognitive effects have been reported in three other studies (23–25).

9.4 Controlled laboratory studies of chronic cannabis users

Research studies in the late 1980s and 1990s improved upon the earlier studies of chronic cannabis users by using control groups, verifying abstinence from cannabis before testing, and quantifying the quantity, frequency and duration of cannabis use (Solowij, 1998). More effort was also made to relate specific cognitive processes to quantity, frequency and duration of cannabis use.

A study by Block and colleagues (26) addressed the concern that cannabis users had poorer cognitive ability than controls *before* they started using cannabis. Block et al matched their user and nonuser samples in their scores on the Iowa Tests of Basic Skills collected in the fourth grade of high school, ensuring that the two groups did not differ in intellectual abilities before they began using cannabis. Block and colleagues compared 144 cannabis users, 64 of whom were light users (less than 4 times per week for 5.5 years) and 80 heavy users (5 or more times per week for 6.0 years) with 72 controls aged 18-42. Twenty-four hours of abstinence was required prior to testing. The results showed that heavy cannabis users performed more poorly on tests of verbal expression and mathematical skills on the 12th grade Iowa test.

Solowij et al (27–29) studied the effects of long-term cannabis user's ability to exclude irrelevant stimuli when concentrating their attention on a task. Solowij assessed attentional processes in long-term cannabis users using a combination of performance

and brain event-related potential (ERP) measures as markers of underlying cognitive processes. She measured the amplitude and latency of ERP components that have been shown to reflect various stages of information processing.

Solowij et al (27) studied 9 cannabis users aged 19–40 who had used cannabis for 11 years for an average of 5 days per week. They were matched on age, sex, years of education and alcohol consumption with 9 controls who had either never used or had used cannabis fewer than 15 times in their lives. Subjects were excluded if they had a history of head injury, neurological or psychiatric illness, had used other drugs, or had high levels of alcohol consumption. The groups did not differ in premorbid IQ estimated by the NART score (30). Cannabis users were asked to abstain from cannabis and alcohol for 24 hours prior to testing and were urine tested to ensure that they did so.

Subjects performed an auditory selective attention task in which random sequences of tones varying in location, pitch and duration were presented through headphones while brain electrical activity (EEG) was recorded. They were asked to attend to a particular pitch presented in particular ear, and to respond to long duration tones by pressing a button. Cannabis users performed significantly more poorly than controls, with fewer correct detections, more errors and longer reaction times. They were less able than controls to filter out irrelevant information, suggesting that long-term cannabis use impaired the ability to efficiently process information.

In a second study Solowij et al (28, 29) assessed relationships between degree of impairment and the frequency and duration of cannabis use. Thirty-two cannabis users were divided into four groups of equal size (N = 8) defined by frequency (light: 2 or fewer times per week versus heavy: more than 3 times per week) and duration (short: 4 or fewer years of use versus long: 5 or more years of cannabis use). Subjects were matched to a group of nonuser controls (N = 16). The cannabis users performed worse than the controls and the greatest impairment was in the heavy user group. The long duration user group found it harder to ignore irrelevant stimuli than the short duration users and controls who did not differ. This impairment increased with the number of years of use but it was not related to frequency of use. There were no differences between groups defined on frequency of use on this measure. Speed of information processing was related to frequency of cannabis use but not to duration of use.

Solowij (31) assessed whether these ERP changes in long-term cannabis users persisted after extended abstinence from cannabis. She studied 32 former users who had used cannabis for a mean of 9 years and who had been abstinent for a mean of 2 years. She found some partial recovery of functioning: the speed of information processing was not reduced in the ex-users but their ability to ignore irrelevant stimuli remained impaired. The degree of impairment increased with the length of cannabis use and was unrelated to the length of abstinence.

Supportive evidence was provided by a NIDA funded study by Struve and colleagues of CNS changes in chronic cannabis users. This research found evidence of larger changes in EEG frequency, primarily in frontal-central cortex, in daily cannabis users of up to 30 years duration compared to short term users and nonusers (32). The results also

suggested that the EEG changes increased with the number of years of daily cannabis use. The major limitation of this research is that changes in frequency of EEG spectra have not been shown to be related to cognitive functioning.

This research group also assessed cognitive functioning (33–35) in subjects screened for current or past psychiatric and medical disorders and CNS injury. Daily cannabis users who had at least 3 years of use were compared to a group who had used daily for 6-14 years, a group who had used on a daily basis for 15 years or more, and a nonuser control group. Sample sizes averaged 15 per group. They reported a dose-response relationship between test performance and intensity of cannabis use, with controls performing best, followed by short term daily cannabis users, with the poorest performance in the very long-term group (33–35).

Pope and Yurgelun-Todd (36) compared the cognitive performance of heavy and light cannabis using college students. The heavy users (n = 65) had used for at least 2 years, on 28 of the past 30 days, and had cannabinoids in their urine. The light users (n = 64) had used no more than 3 days in the past month and had no cannabinoids in their urine. The authors used this design because they argued that infrequent users would 'differ less from heavy users on some possible confounding variables than would control subjects who had never used cannabis at all, while still differing sharply from heavy users on ... extent of recent cannabis use' (p 521).

Subjects were admitted overnight to a hospital ward to ensure that they were abstinent from cannabis at least 19 hours before being tested. The two groups did not differ on any social or demographic variables, except that heavy users came from more affluent families and scored more poorly on Verbal IQ and self-reported Scholastic Aptitude Tests. These differences were statistically adjusted for when comparing the two groups on the neuropsychological tests. The groups did not differ on tests of digit span, auditory sequential processing, the Stroop Test or the Wechsler Memory Scale. They differed on tests of attention (the Wisconsin test, the Benton VFT, and the CLVT) and these differences persisted when adjusted for differences in verbal IQ, self-reported SAT score and other drug use.

9.5 Epidemiological evidence

Lyketsos et al (37) reported a large-scale prospective epidemiological study of the effect of cannabis use on cognitive functioning. They followed up 1318 adults 11.5 years after they were assessed on the Mini Mental State Exam (MMSE) and assessed cognitive decline on the MMSE. They also inquired about use of cannabis, alcohol and tobacco. Their study came close to meeting the criteria for an optimum study specified by Pope et al (38), namely, it was a longitudinal study using a large sample of people from the general population who were assessed on cognitive performance and on cannabis and other drug use. Lyketsos et al found that the mean MMSE score declined by 1.2 points over 11.5 years and the decline was greater among older participants. There was, however, no relationship between cannabis use and the decline in MMSE score, and this lack of relationship persisted when adjustments were made for age, sex, education, minority status and use of alcohol and tobacco.

The Lyketsos et al study supports other evidence that cannabis use does not produce *gross* impairment of cognitive function but for a number of reasons it does not exclude the possibility that cannabis use causes more subtle cognitive impairment. First, only 57% of those initially interviewed were followed up and those lost to follow up had poorer MMSE scores at first assessment. Second, the MMSE is a screening test for gross cognitive impairment; it is not sensitive to small changes in cognitive functioning (39). Third, more than two weeks daily use at any of the three assessments qualified as 'heavy cannabis use'. Since cannabis use declines steeply with age (40) very few of this sample were likely to be daily cannabis users for any length of time.

9.6 Studies of neurotoxicity

Human studies of brain anatomy have generally failed to find signs of gross 'brain damage' after chronic use of cannabis (19, 41). The human studies of cognitive functioning suggest that cannabis may produce more subtle changes in brain function that existing methods of brain imaging are not sufficiently sensitive to detect (19). Wert and Raulin (41) proposed, that on the available evidence 'there are no gross structural or neurological deficits in marijuana-using subjects, although subtle neurological features may be present' (p.624).

9.7 Summary

The 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 some evidence that daily cannabis use over many years may produce more subtle impairment in memory, attention and the organisation and integration of complex information. This evidence suggests that these forms of cognitive impairment increase with the duration of cannabis use. It remains to be seen whether the impairment can be reversed by an extended period of abstinence.

Well controlled studies using sophisticated methods of investigation have failed to demonstrate gross structural change in the brains of heavy, long term cannabis users. These negative results are consistent with the evidence that any cognitive effects of chronic cannabis use are subtle, and hence unlikely to be manifest as gross structural changes in the brain.

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10 Cannabis use and psychotic disorders

There is reason to suspect that cannabis use may be a cause of psychotic disorders, i.e. mental illnesses in which sufferers experience hallucinations and delusions and show impaired reality testing. THC produces symptoms found in some psychotic disorders, namely, euphoria, distorted time perception, and cognitive and memory impairments (1, 2). In laboratory studies normal volunteers given high doses of THC have reported visual and auditory hallucinations, delusional ideas, thought disorder, and symptoms of hypomania (3, 4). A 'cannabis psychosis' has been reported by clinical observers in countries with a long history of heavy cannabis use, such as India and Egypt (1, 5).

We need to distinguish two hypotheses about possible relationships between cannabis use and psychosis (6). The strongest causal hypothesis is that heavy cannabis use can cause a 'cannabis psychosis', that is, a psychosis would not occur in the absence of cannabis use and in which the causal role of cannabis can be inferred from the symptoms and their relationship to cannabis use (being preceded by heavy cannabis use and remitting after abstinence).

A second hypothesis is that cannabis use can precipitate an episode of schizophrenia. According to this hypothesis, cannabis use is one factor among many others (including genetic predisposition and other unknown causes) that bring about schizophrenia, a psychotic disorder which becomes chronic in a substantial proportion of those who develop it.

If cannabis use can precipitate schizophrenia it is also likely that it can exacerbate the symptoms of the disorder. Even if cannabis use does not precipitate schizophrenia, its use may exacerbate symptoms of schizophrenia either directly, by affecting the dopaminergic system in the brain, or indirectly, by reducing compliance with, or interfering with the effects of, the neuroleptic drugs used to treat its symptoms.

In order to infer that cannabis use is a cause of psychosis in any of these ways we need evidence: that cannabis use and psychosis are associated; that chance is an unlikely explanation of the association; that cannabis use preceded the psychosis; and that plausible alternative explanations of the association can be excluded (7). As we will see, there is evidence that cannabis use and psychosis are associated, that chance is an unlikely explanation of the association, and that cannabis use often precedes psychoses. The most difficult task is excluding the hypothesis that the relationship between cannabis use and psychosis is due to other factors (e.g. other drug use, or a genetic predisposition both to develop schizophrenia and use cannabis).

10.1 'A cannabis psychosis'

Case reports of 'cannabis psychoses' (8–11) describe individuals who develop psychotic symptoms or disorders after using cannabis. Chopra and Smith (9), for example, described 200 patients who were admitted to a psychiatric hospital in Calcutta between

1963 and 1968 with psychotic symptoms following the use of cannabis. The most common symptoms 'were sudden onset of confusion, generally associated with delusions, hallucinations (usually visual) and emotional lability ... amnesia, disorientation, depersonalisation and paranoid symptoms' (p. 24). Most psychoses were preceded by the use of large doses of cannabis. Chopra and Smith argued that heavy cannabis use was not a sign of pre-existing disorders because a third of their cases had no prior psychiatric history, the symptoms were remarkably uniform regardless of prior psychiatric history, and those who used the most potent cannabis preparations experienced psychoses after the shortest period of use.

The findings of Chopra and Smith have received some support from other smaller case series that suggest that large doses of potent cannabis products can be followed by a 'toxic' psychotic disorder with 'organic' features of amnesia and confusion. These disorders have been reported from the Caribbean (12), New Zealand (13), Scotland (11), South Africa (10), Sweden (8), the United Kingdom (14) and the United States (15).

These disorders have been attributed to cannabis use for the following reasons: the onset of the symptoms followed closely the ingestion of large quantities of cannabis; the affected individuals often exhibited 'organic' symptoms, such as confusion, disorientation and amnesia; some had no personal or family history of psychoses before using cannabis; their symptoms rapidly remitted after abstinence from cannabis use, usually within several days to several weeks; recovery was usually complete with the person having no residual psychotic symptoms; and the disorder only recurred if the individual resumed cannabis use (16).

Sceptical author (2, 17) have criticized the poor quality of information in these studies on: cannabis use; its relationship to the onset of psychosis; the person's premorbid adjustment; and their family history of psychosis. They also emphasize the variety of clinical pictures of 'cannabis psychoses' reported by different observers. These weaknesses impair the value of these case series.

10.1.1 Controlled studies

A small number of controlled studies have been conducted over the past 20 years (18–22). Some studies have either compared persons with 'cannabis psychoses' with persons who have schizophrenia, or compared psychoses occurring in persons who do and do not have biochemical evidence of cannabis use prior to presenting for treatment. Their results have been mixed, in part because of the small sample sizes in studies that have failed to replicate positive findings, and because of variations in the research methods (16).

Several studies have examined the relationship between cannabis use and psychotic symptoms in the general population. Tien and Anthony (23) used data from the Epidemiologic Catchment Area study to examine the relationship between drug use and reports of one or more of 11 'psychotic experiences' during a twelve-month period (4 types of hallucinations and seven types of delusional belief). They compared 477 cases who reported one or more psychotic symptoms with 1818 controls who did not. Cases and controls were matched for age and social and demographic characteristics. Daily cannabis use was found to double the risk of reporting a psychotic symptom (after statistical adjustment for alcohol use and psychiatric diagnoses at baseline).

Thomas (24) reported the prevalence of psychotic symptoms among cannabis users in a random sample of people in a large city in the North Island of New Zealand. One in seven (14%) cannabis users reported 'strange, unpleasant experiences such as hearing voices' or 'becoming convinced that someone is trying to harm you or that you are being persecuted' after using cannabis.

The National Survey of Mental Health and Well-Being (NSMHWB) conducted in Australia in 1997 included a screening questionnaire for the presence of psychotic symptoms (25). Among those under 50 years of age who screened positive for a psychotic disorder, 8% (n = 27) met criteria for cannabis dependence in the past 12 months. This was 17% of all persons diagnosed with cannabis dependence (26). After adjusting for demographics, affective and anxiety disorders, smoking status and alcohol dependence, a diagnosis of cannabis dependence doubled the odds of reporting psychotic symptoms (27).

10.1.2 Overall evaluation

The hypothesis that there is a 'cannabis psychosis' is still contentious. In its favour are the equivocal evidence from the case series and the small number of positive controlled studies. Critics of the hypothesis emphasize the poor quality of the clinical judgments about aetiology, the poorly specified criteria used in diagnosing these psychoses, the dearth of controlled studies, and the striking variations in the clinical features of these 'cannabis psychoses'.

It is a plausible hypothesis that high doses of cannabis can produce psychotic *symptoms* but the evidence for a 'cannabis psychosis' as a specific clinical syndrome is much less compelling because the symptoms reported by different observers have been so mixed (28). If cannabis-induced psychoses exist, they are either rare or they only rarely receive medical intervention in Western societies. The total number of cases of putative 'cannabis psychoses' in the 12 case series reviewed in [illegible] (16) was 397 and 200 of these came from a single series collected over 6 years from a large geographic area in which heavy cannabis use was endemic (9).

10.2 Cannabis use and schizophrenia

10.2.1 Clinical studies

In case-control studies (29, 30), schizophrenic patients are more likely to have used psychotomimetic drugs such as amphetamines, cocaine, and hallucinogens than other psychiatric patients, normal controls or the general population (31). Variations in rates of use between studies reflect differences in the sampling of patients, with younger patients reporting higher rates than older persons with chronic disorders. Studies have also differed in the criteria for diagnosing schizophrenia and the manner in which substance use has been assessed (32).

Alcohol use, abuse and dependence are probably more common in the schizophrenic population than in the general population (33, 34) but findings on cannabis use have been more mixed (16). Generally, cannabis is the most commonly used drug after

alcohol and tobacco, and it is often used with alcohol (32, 35, 36). An Australian study of a clinical sample of persons with schizophrenia (37) has broadly confirmed the pattern of substance use and abuse in American studies, finding alcohol the most commonly abused substance (18% abuse or dependence in the past 6 months), followed by cannabis (13% abuse or dependence in the past 6 months).

The controlled clinical studies disagree about the correlates of substance abuse in schizophrenia. Most have found that young males are over-represented among cannabis users (16), as they are in the general community (38). In some studies, substance users have been reported to have an earlier onset of psychotic symptoms, a better premorbid adjustment, more episodes of illness, and more hallucinations (36, 39, 40) but other well controlled studies have failed to replicate some or all of these findings (41–43).

10.2.2 Population studies

Surveys of psychiatric disorders in the community have reported higher rates of substance abuse disorders among persons with schizophrenia. In the ECA study (44) nearly half of the patients identified as schizophrenic had a diagnosis of substance abuse or dependence (34% for an alcohol disorder and 28% for another drug disorder) (45). These rates were higher than the rates in the general population, namely, 14% for alcohol disorders (46) and 6% for drug abuse (44). Cuffel et al (42) reported that the most commonly used substances among persons with schizophrenia in the ECA study were: alcohol (37%) and cannabis (23%), followed by stimulants and hallucinogens (13%). The most common combination was alcohol and cannabis (31%). These findings have also been replicated in a similar survey in Edmonton, Alberta (47).

In the Australian National Survey of Mental Health and Well-Being (NSMHWB), cannabis use and a positive screen for psychosis were associated. Among those under 50 years of age who reported that they had received a diagnosis of schizophrenia, 12% met ICD-10 criteria for a cannabis use disorder in the past 12 months and 21% met criteria for an alcohol use disorder. After adjusting for other disorders and unemployment status, those who met criteria for ICD-10 cannabis dependence were 2.9 times more likely to report that they had been diagnosed with schizophrenia than those without cannabis dependence (26).

A high rate of cannabis use was also reported in the Low Prevalence Study (LPS) of psychoses in the Australian cities of Perth, Melbourne, Brisbane and Canberra (48). In this study persons with a suspected psychotic disorder were assessed by experienced clinicians using ICD-10 criteria, (48) including significant proportions who were not in domestic dwellings (which was a limitation of the NSMHWB sample) (26). One in four (24%) were daily cannabis users, 30% met lifetime criteria for alcohol abuse or dependence and 25% met lifetime criteria for cannabis abuse or dependence (48).

10.3 Explaining the association

One hypothesis is that cannabis use precipitates schizophrenic disorders in vulnerable persons. Its supporters cite the earlier age of onset of psychotic symptoms among persons with schizophrenia who use cannabis and reports that they have better premorbid adjustment, fewer negative symptoms, and a better treatment response (49).

A second possibility is that the association between cannabis use and an acute onset of schizophrenia is spurious. It may be, Arndt et al (39) argue, that schizophrenics with a better premorbid personality are more likely to be exposed to illicit drug use than persons with schizophrenia who are socially withdrawn. There is supportive evidence (50) that persons with acute onset psychoses usually have a better premorbid adjustment and a better prognosis. They also have greater opportunities to use cannabis and other illicit drugs than persons who are socially withdrawn.

A third possibility is that cannabis use is a consequence (rather than a cause) of schizophrenia. For example, cannabis and other drugs may be used to medicate the unpleasant symptoms of schizophrenia (51), such as depression, anxiety, lethargy, and anhedonia, or the unpleasant side effects of the neuroleptic drugs that are often used to treat the disorder (40).

10.3.1 Precipitation of schizophrenia

The most convincing evidence that cannabis use may precipitate schizophrenia comes from a 15-year study of cannabis use and schizophrenia in 50,465 Swedish conscripts (52). This study investigated the relationship between self-reported cannabis use at age 18 and receiving a diagnosis of schizophrenia in the next 15 years (as indicated by the Swedish psychiatric case register). Andreasson et al found that those who had tried cannabis by age 18 were 2.4 times more likely to be diagnosed with schizophrenia than those who had not. The more often cannabis had been used by age 18 the more likely they were to receive this diagnosis. The rate of a schizophrenia diagnosis was 1.3 times higher among those who had used cannabis one to ten times, 3 times higher among those who had used cannabis between one and fifty times, and 6 times higher among those who had used cannabis more than fifty times.

These risks were substantially reduced after statistically adjusting for variables that were related to the risk of developing schizophrenia, namely, having a psychiatric diagnosis at conscription, and having parents who had divorced (as an indicator of parental psychiatric disorder). Nevertheless, the relationship remained statistically significant. The risk of a diagnosis of schizophrenia was still 1.5 times greater for those who had smoked cannabis from one to ten times, and 2.3 times greater for those who had used ten or more times. Andreasson et al (52) and Allebeck (49) have argued that this indicates that cannabis use precipitates schizophrenia in vulnerable individuals.

A number of alternative explanations have been offered of the Swedish finding. First, there was a large gap between self-reported cannabis use at age 18 and the development of schizophrenia over the next 15 years (53). The diagnosis of schizophrenia was based upon a case register so there was no data on how many individuals were using cannabis at the time that their schizophrenia was diagnosed. Andreasson et al argued that cannabis use persisted because use at age 18 was strongly related to a diagnosis of drug abuse.

A second possibility is that schizophrenia was misdiagnosed. On this hypothesis, the higher rate of 'schizophrenia' among the heavy cannabis users was due to cannabis-induced psychoses that were misdiagnosed as schizophrenia (53). Andreasson et al (54) tested this possibility by examining 21 cases of schizophrenia among conscripts in the case register (8 of whom had used cannabis and 13 of whom had not). They found that

80% of these cases met the DSM-III requirement that the symptoms had been present for at least six months, thereby excluding the diagnoses of transient drug-induced psychotic symptoms.

A third hypothesis is that the relationship between cannabis use and schizophrenia is explained by the use of other drugs. Studies show (see chapter 5) that heavy cannabis users in late adolescence are more likely to use other illicit drugs, including amphetamine, which can produce an acute psychosis (55). Amphetamines were the most commonly used illicit drugs in Sweden during the late 1960s and early 1970s (56). On this hypothesis, amphetamine-induced psychoses would produce a spurious association between cannabis use and schizophrenia. The evidence that psychotic symptoms persisted beyond 6 months (54) also makes this an unlikely hypothesis.

A fourth hypothesis is that early cannabis use was a symptom of emerging schizophrenia. Andreasson et al (54) rejected this hypothesis, noting that the cannabis users who developed schizophrenia had better premorbid personalities, a more abrupt onset, and more positive symptoms than the non-users of cannabis. Moreover, there was still a dose-response relationship between cannabis use and schizophrenia among those who had no previous psychiatric history. The persuasiveness of this evidence depends upon whether a *failure* to identify a psychiatric disorder at conscription meant that no disorder was present.

A fifth hypothesis depends upon under-reporting of cannabis use at conscription. Andreasson et al (52) acknowledged that cannabis use was probably under-reported because this information was not collected anonymously. They argued, however, that under-reporting would *under*-estimate the relationship between cannabis use and schizophrenia. This is true if the schizophrenic and non-schizophrenic conscripts were equally likely to under-report. If, for example, pre-schizophrenic subjects were more candid about their drug use, then the apparent relationship between cannabis use and schizophrenia could be spurious (53). This seems unlikely, however, in view of the relationship between the *frequency* of cannabis use by age 18 and the risk of a schizophrenia diagnosis among heavy users.

10.3.2 Exacerbation of schizophrenia

Clinical reports suggest that schizophrenic patients who continue to use cannabis experience more psychotic symptoms (57), respond poorly to neuroleptic drugs (58), and have worse clinical outcomes than those patients who do not (59). These reports have been supported by controlled studies.

Negrete et al (60) conducted a retrospective study of the relationship between self-reported cannabis use and symptoms in the clinical records of 137 schizophrenic patients who had the disorder for at least six months. They found higher rates of hallucinations and delusions and more hospitalisations among patients who were cannabis users. These relationships persisted after statistical adjustment for age and sex. Similar findings have been reported by Cleghorn et al (61) who found that cannabis was the most heavily used drug, and drug abusers had higher rates of hallucinations, delusions and positive symptoms than those who did not abuse drugs. DeQuardo et al (62) reported similar findings in a retrospective study of 67 schizophrenic patients.

Jablensky et al (63) reported a two year follow-up of 1202 first episode schizophrenic patients enrolled in 10 countries as part of a WHO Collaborative study. They found that the use of 'street drugs', including cannabis and cocaine, was associated during the follow up period with more psychotic symptoms and hospitalisation. Martinez-Arevalo et al (64) reported in a study of 62 schizophrenic patients that those who used cannabis during a one-year follow up were more likely to relapse and comply poorly with drug treatment. Caspari (65) reported similar findings in a six year follow up study of 39 schizophrenic patients with a history of cannabis abuse and 39 schizophrenic patients without such a history.

Linszen et al (66) reported a prospective study of 93 psychotic patients whose symptoms were assessed monthly over a year. Twenty-four of these patients were cannabis abusers (11 were less than daily users and 13 were daily cannabis users). The cannabis users relapsed to psychosis sooner, and had more relapses in the year of follow up, than the patients who had not used cannabis. Daily users relapsed earlier, and more often, than the less than daily users who, in turn, relapsed sooner, and more often, than the patients who did not use cannabis. These relationships persisted after statistically controlling for premorbid adjustment, and alcohol and other drug use.

Two uncertainties remain. First, it may be that schizophrenia patients who do and do not use cannabis differ in premorbid personality, family history, and other characteristics. This explanation is unlikely in the WHO schizophrenia study (63) and the Linszen et al study (66), both of which used statistical methods to adjust for these confounders. The second difficulty is separating the contributions that cannabis and other drugs make to the exacerbation of schizophrenic symptoms. Heavy alcohol use is common among persons with schizophrenia, and the heavier their cannabis use, the more likely the person is to use psychostimulants and hallucinogens (32). Only Linszen et al statistically adjusted for the effects of concurrent alcohol and drug use. Our confidence that the effect is attributable to cannabis will increase with replications of the Linszen et al study.

10.3.3 Intervention studies

If cannabis use exacerbates schizophrenia then patients who reduce their cannabis use should have fewer symptoms and lower relapse rates. The major difficulty with testing this prediction is getting persons with schizophrenia to reduce their cannabis use. Dependence on alcohol and other drugs is difficult to treat (67), and persons with schizophrenia often have characteristics that predict a poor treatment outcome, namely, they lack social support, they may be cognitively impaired, they are often unemployed, and they may comply poorly with treatment (32, 68).

There are very few controlled outcome studies of substance abuse treatment in schizophrenia (69). Few of these have produced large enough benefits of treatment, or treated a large enough number of patients, to provide an adequate chance of detecting any positive impacts of abstinence on the course of disorders. The few that have been large enough (70) have not reported results separately by diagnosis. Better designed intervention studies should help to clarify the relationship between cannabis use and schizophrenia.

10.3.4 Self-medication

The evidence for the self-medication hypothesis (that persons with schizophrenia use cannabis to avoid unpleasant symptoms of the illness) is not very compelling. Persons with schizophrenia report that they use alcohol, cannabis and other illicit drugs for similar reasons to persons who do not have schizophrenia, namely, to relieve boredom, to provide stimulation, to feel good, and to socialize with peers (32, 37, 71, 72). The drugs that are most often used by schizophrenic patients are also those that are most readily available in the general population, namely, tobacco, alcohol, and cannabis.

In favour of the self-medication hypothesis is the evidence that some schizophrenic patients report using cannabis for its euphoric effects and to relieve negative symptoms and depression (e.g. (29, 40, 73)). Dixon et al (40), for example, surveyed 83 patients with schizophrenia who reported that cannabis reduced anxiety and depression, and increased a sense of calm, but at the cost of making them feel more suspicious.

Hamera et al (74) examined correlations over 84 consecutive days between self-reported psychotic symptoms, licit and illicit drug use, and medication use in 17 persons with schizophrenia. They found relationships between nicotine and prodromal psychotic symptoms and between caffeine use and symptoms of anxiety and depression but there were no relationships between psychotic symptoms and alcohol or cannabis use. This study does have limitations. The difficulty of the self-monitoring task probably selected patients who were more compliant than a representative sample of schizophrenics and they reported low rates of drug use. It is also possible that the time period of 84 days was too short to fully examine the relationship between drug use and major exacerbations of the illness.

10.4 Summary

Evidence supports the hypothesis that cannabis use exacerbates the symptoms of schizophrenia. This evidence comes from a number of retrospective and prospective studies that have controlled for confounding variables. This hypothesis is also biologically plausible: psychotic disorders involve disturbances in the dopamine neurotransmitter systems (75) and cannabinoids, such as THC, increase dopamine release (76).

It is also possible that cannabis use precipitates schizophrenia in persons who are vulnerable because of a personal or family history of schizophrenia. This hypothesis is consistent with the stress-diathesis model of schizophrenia (50, 77) in which schizophrenia is the result of stress acting upon a genetic 'diathesis' to develop schizophrenia. The only direct evidence for it comes from a study by McGuire et al (21) which reported that schizophrenic patients with a history of heavy cannabis use were 10 times more likely to have a family history of schizophrenia than persons with a psychosis who had not used cannabis.

It remains uncertain whether cannabis use can cause schizophrenia that would not have occurred in its absence (78). If it can, it is unlikely to account for more than a minority of cases. Most of the 274 conscripts in the Andreassen et al study who developed

schizophrenia had not used cannabis (54) and only 21 of those who did were heavy cannabis users. The *treated* incidence of schizophrenia has not increased during the 1970s and 1980s (79), despite very substantial increases in cannabis use among young adults in Australia and North America (38). Although there are complications in interpreting such trends (80), the debate has been about whether the incidence of schizophrenia has *declined* or remained *stationary* rather than *increased* (81).

10.5 References

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11 Is cannabis a gateway drug?

Adolescent cannabis use is an understandable concern to the community. This is because adolescents' decisions about whether or not to use drugs are not as informed as those of adults (1) and regular cannabis use may complicate the transition from childhood to adulthood by interfering with school performance, interpersonal relationships with parents and peers, and limiting important life choices, such as whom and when to marry, and what occupation to pursue (2, 3). Young people who start using cannabis in adolescence are more likely to become regular users and are therefore more likely to experience any adverse health effects caused by chronic cannabis use (e.g. (1, 3). Adolescence is also a time of risk-taking when the use of an intoxicant, such as alcohol or cannabis, while driving a car may increase the risk of accidental injury and premature death (1).

One concern about adolescent cannabis use has dominated the cannabis policy debate. This is that adolescent cannabis use may increase the chance that young people will use other more dangerous illicit drugs, such as cocaine and heroin (4–6). This is known as the 'gateway hypothesis'.

In deciding whether cannabis is a gateway drug the first question that needs to be answered is whether cannabis users are more likely to use other illicit drugs. If so, we need to ask whether the relationship is explained by other factors. One possibility is that individuals who use cannabis are more likely to use other illicit drugs for other reasons. We can test this by seeing whether rates of illicit drug use among cannabis users change when we take account of the characteristics of young people who are the most likely to use cannabis.

If there is a relationship between cannabis and other illicit drug use, we have to explain it. The two main explanations that feature in the public debate are: (1) that cannabis users are more likely to use other illicit drugs because of the pharmacological and other effects that cannabis has; and (2) that cannabis users are more likely to use other illicit drugs because the same black market supplies cannabis and other illicit drugs, so cannabis users are more likely to have access to other illicit drugs.

11.1 Is there a relationship between cannabis use and other drug use?

There is abundant evidence from surveys of adolescent drug use in the United States and elsewhere that *regular* cannabis use and the use of cocaine and heroin are associated (7). From the late 1970s to the 1990s in the United States, there was a strong relationship between regular cannabis use and the later use of heroin and cocaine. Kandel (8), for example, found that only 7% of American adolescents who had not used cannabis reported using another illicit drug. By contrast, 33% of those who reported using cannabis had used another illicit drug. Most (84%) daily cannabis users had done so and they had also used many more types of illicit drugs than their peers who had not used cannabis or who were not daily users of cannabis (8).

The same relationship has been observed in Australian surveys of drug use (9). In the 1993 National Campaign Against Drug Abuse (NCADA) survey of drug use in Australia, for example, even though 96% of cannabis users had *not* used heroin, the odds of using heroin were approximately 30 times higher among those who have used cannabis than those who had not (9). In the 1998 National Drug Strategy Household Survey, there was an even stronger relationship: those who reported that they had ever used cannabis were 78 times more likely to report having used heroin. The association is so strong because so few persons who have used heroin had not used cannabis (only 4 out of 276 in the 1998 survey).

Kandel and colleagues have described a typical sequence of involvement with licit and illicit drugs among American adolescents during the 1970s and 1980s. Almost all adolescents who have tried cocaine and heroin, had used alcohol, tobacco and cannabis in that order (10). Those who began to use alcohol and tobacco at an early age, and those who became regular smokers and drinkers, were the ones who were most likely to use cannabis. In turn, it was cannabis users who began use at an early age who were the most likely to become regular cannabis users and the most likely to use hallucinogens, amphetamines and tranquillisers. The heaviest users of these drugs were, in turn, more likely to use cocaine and heroin. Kandel and her colleagues have confirmed these results in longitudinal studies of adolescent drug use in this age cohort (11) and in later cohorts with high rates of crack cocaine use (12, 13).

Generally, the earlier the age at which a young person used any drug in the sequence, and the more regular their use of it, the more likely they were to use the next drug in the sequence (14–16). This sequence of drug involvement has largely been confirmed by other US researchers (7, 17). Longitudinal studies of drug use in Australia (18), Germany (19), New Zealand (20–23), and Sweden (24, 25) have broadly confirmed US findings on sequences of drug involvement and predictors of progression to cannabis and other illicit drug use.

11.2 Is the relationship between cannabis and other drug use spurious?

One explanation of the relationship between daily cannabis use and the use of other drugs is that it is due to the type of person who uses cannabis. According to this 'selective recruitment' hypothesis, the relationship is explained by the recruitment to cannabis use of deviant and nonconformist young persons who have a predilection to use a range of intoxicating drugs like alcohol, cannabis, cocaine and heroin (22). On this hypothesis, the order in which these drugs are tried simply reflects their availability and the societal disapproval of their use (7, 17). That is, alcohol and tobacco use precede cannabis use because alcohol and tobacco are readily available to adolescents, and cannabis use precedes heroin and cocaine use because cannabis is the much commonly used illicit drug and it is more readily available than cocaine and heroin. On this hypothesis, cannabis use is not a cause of the use of other illicit drugs. Rather, cannabis and other illicit drug use are common consequences of pre-existing social deviance and nonconformity (26, 27).

The selective recruitment hypothesis is supported by the substantial correlations between various types of nonconforming adolescent behaviour, including high school drop out, early sexual experience and unplanned pregnancy, delinquency, and alcohol and illicit drug use (28, 29). All of these behaviours are correlated with nonconformist and rebellious attitudes and antisocial conduct in childhood (30) and early adolescence (27, 28).

Regular cannabis users are more likely than their peers: to have a history of antisocial behaviour (23, 31); to be nonconformist and alienated (30–32); to perform more poorly at school (33–35); and to use drugs to deal with personal distress (30, 36). In general, the more of these risk factors that adolescents have, the more likely they are to use cannabis daily, and to use other illicit drugs (31, 37, 38).

The selective recruitment hypothesis can be tested in longitudinal studies by examining whether cannabis use still predicts the use of heroin and cocaine after statistically controlling for pre-existing differences between cannabis users and nonusers in social deviance and non-conformity (22). A number of studies have used this strategy to test the selective recruitment hypothesis.

Yamaguchi (39) tested whether the relationship between cannabis use and 'harder' illicit drug use persisted after statistically controlling for pre-existing adolescent behaviours and attitudes, interpersonal factors, and the age of initiation into drug use. They found that the relationship between cannabis use and the use of other illicit drugs was not explained by these factors or by friends' cannabis use. The same finding has emerged in several other studies (11, 40, 41). In these studies, the relationship between cannabis and heroin use has been reduced but not eliminated by statistically controlling for differences between users and non-users of cannabis.

O'Donnell and Clayton (40) have argued that this is strong evidence in favour of a causal connection between cannabis and heroin use. The strength of their argument depends on whether the most important characteristics of cannabis users have been statistically controlled for in these studies. It would be difficult to argue that this was true in the early studies. Kandel et al. (11), for example, were unable to measure the users' attitudes and family characteristics at the time of drug initiation. In the O'Donnell and Clayton (40) and Robins et al. (41) studies, deviance 'prior' to drug use was assessed retrospectively, with unknown validity. Baumrind (42) argued that 'in the absence of evidence of external validity' of these measures it is 'safer' to assume that the relationship between cannabis use and heroin use is spurious.

Two studies by Fergusson and Horwood (20, 22) address many of the weaknesses in the earlier studies. These report data from a prospective study of 990 New Zealand children who were followed from birth to age 21 years and assessed on a wide range of psychosocial variables that potentially explain the relationship between cannabis use and the use of other illicit drugs. These included: family background (socio-economic status, parental conflict and divorce, childhood sexual abuse, parental punishment and parental attachment); parental adjustment (parental alcohol and drug problems, criminality and illicit drug use); individual characteristics of the young person (gender, intelligence, novelty seeking); early adolescent development (cigarette smoking, frequency of alcohol

use, juvenile offending, school drop out, conduct problems and attitudes towards drug use); peer affiliations (peer use and problems with alcohol and other drug use); and personal history of risk taking. These factors were statistically controlled for in analyses of relationships between cannabis use and use of other illicit drugs.

Fergusson and Horwood (20) reported on the relationship between the use of cannabis by age 16 and the use of other illicit drugs by the age of 18 years. They found a strong relationship between the frequency of cannabis use by age 16 and development of a problem with cannabis, alcohol or other substances by age 18. Early cannabis users came from lower socio-economic status families with a history of parental conflict, parental criminality and alcohol and drug use and low parental attachment. They also had a personal history of conduct problems, low self-esteem, high novelty seeking, and high affiliation with delinquent peers. Adjustment for these factors reduced but did not eliminate the relationship between early cannabis use and the use of other illicit drugs.

Fergusson and Horwood (22) reported a later follow up of the cohort. They found that 69% of their sample reported using cannabis by age 21, and 26% had used one or more other illicit drugs, with 4% having used cocaine or an opiate. In 99% of cases, cannabis use preceded the use of other illicit drugs. They found a strong relationship between level of cannabis use at any age and the use of another illicit drug. Compared to those who had never used cannabis, the risk of using another illicit drug was around 4 times higher among those who had used cannabis once or twice, 12 among those who had used 3 to 11 times, 41 times higher among those who had used 12 to 49 times and 143 times greater among those who had used 50 times or more. The relationships were reduced but remained substantial when other psychosocial factors were controlled for statistically. Compared to non-users of cannabis, the risks (after statistical adjustment) were 3 greater for those who had used once or twice, 8 greater for those who had used 3 to 11 times, 21 greater for those who had used 12 to 49 times and 59 greater for those who had used for 50 times or more.

The results of the Fergusson and Horwood studies make it unlikely that selective recruitment wholly explains the relationship between cannabis use and other illicit drug use. But its findings do not, as Fergusson and Horwood acknowledge, rule out other explanations. Among these is the possibility that there is a shared genetic vulnerability to use and become dependent on cannabis and other illicit drugs.

Studies of alcohol, tobacco and other drug use in identical and non-identical twins indicate that there is a genetic vulnerability to developing dependence on alcohol (43), cannabis (44) and tobacco (45). More importantly, a component of the genetic vulnerability to dependence on these three drug classes is shared or common (46). So too are the shared family and environmental factors that influence alcohol and cannabis dependence (46). The contribution of genes to dependence on other illicit drugs is less certain because rates of use in these twin studies have been too low to provide a powerful test of this hypothesis. The hypothesis of common genes for regular use of cannabis and other illicit drugs has not been directly tested in any of the cohort studies, including that of Fergusson and Horwood. The identification of specific candidate genes for vulnerability to drug dependence will enable this hypothesis to be tested in future studies.

11.3 Explaining the association between cannabis and other drug use

If the association between cannabis and heroin use is not explained by pre-existing differences between cannabis users and nonusers, how might cannabis use 'cause' heroin and cocaine use? The two main competing explanations differ in whether they attribute the relationship to the pharmacological effects of cannabis or to the social context within which cannabis is obtained and used.

One hypothesis is that the pharmacological effects of cannabis use predispose regular cannabis users to use other intoxicating drugs (47, 48). Nahas (47) has hypothesised that 'the biochemical changes induced by marijuana in the brain result in a drug-seeking, drug-taking behaviour, which in many instances will lead the user to experiment with other pleasurable substances' (p xxiii).

Recent studies in animals (e.g. 49) have been interpreted as supporting a pharmacological explanation of the association between regular cannabis use and other drug use (50). These studies indicate that common biochemical pathways underlie the rewarding effects of cannabis, cocaine, heroin and nicotine (51). All these drugs appear to act on dopaminergic neurotransmitter systems that are involved in the 'reward centres' in an area of the midbrain, the nucleus accumbens (52). However, there is as yet no direct evidence from animal studies that administration of THC to animals increases their risk of using other illicit drugs (53).

Pharmacological explanations of the relationship between cannabis and other drug use also have difficulty explaining a number of facts about their relationship. First, there are relatively low rates of progression from cannabis use to the regular use of other illicit drugs; experimentation and discontinuation of cannabis use is the norm (54). Those heavy cannabis users who do use other illicit drugs also continue to use cannabis, as well as the new illicit drugs. As Donovan and Jessor (17) have noted: '...'harder' drugs do not serve as substitutes for 'softer' drugs. Rather, a deepening of regular substance use appears to go along with a widening of experience in the drug domain' (p. 548–549). This pattern of involvement is more consistent with a genetic vulnerability to drug dependence than the hypothesis that cannabis use is a stepping-stone to experimentation with other drugs.

Third, the pattern of progression in drug use among American adolescents in the 1970s was affected by drug availability (14). Among cohorts of heroin users in the 1950s and 1960s, cannabis use was confined to those geographic areas of the US in which it was readily available (5). Research on African-American adolescents also showed a variation in the sequence of drug use. In African-American communities cocaine and heroin were more readily available than hallucinogens so cocaine and heroin use often preceded the use of hallucinogens (14). Similarly, American soldiers in Vietnam used heroin before they used alcohol because heroin was cheaper and more freely available in Vietnam than was alcohol (since many of the American troops were under the legal drinking age of 21) (55).

The historical and geographical variations in sequences of drug use suggest sociological explanations of the use of heroin among heavy cannabis users. One hypothesis is that regular cannabis use predicts an increased use of other illicit drugs because regular cannabis users have an increased contact with other drug users and drug sellers and hence more opportunities to use other illicit drugs than peers who do not use cannabis regularly. Regular cannabis use thereby increases involvement in a drug using subculture which, in turn, exposes cannabis users to peers who have used other illicit drugs, who approve of such drug use, and who provide more opportunities to use other illicit drugs because of their increased availability within their social circle (5, 56).

Although plausible, there is little direct evidence on the drug subculture hypothesis. Goode (5) presented data from the late 1960s indicating that the number of friends who used heroin was a stronger predictor of heroin use than was frequency of cannabis use, arguing that the 'correlation between frequency of use and the use of dangerous drugs ... [is] the result of interaction and involvement with others who use' (p. 332). These observations have been supported by Kandel's (8) finding that the strongest predictor of continued cannabis use in early adulthood was the number of friends who were cannabis users.

Fergusson and Horwood's (22) analysis of the Christchurch Child Development Study was able to examine the contribution of affiliation with drug using peers to the relationship between cannabis and other illicit drug use. They included self-reported peer use of alcohol, cannabis and other illicit drugs in their statistical analyses. Their inclusion reduced but did not eliminate the relationship between cannabis and other illicit drug use, indicating that while peer drug use made a contribution to the association, it did not fully explain it.

The role of socialisation in a drug-using subculture and involvement in drug markets has not been directly tested in the important cohort studies (22). It is nonetheless a plausible hypothesis. Regular cannabis users are distinguished from non-users by their extensive social relationships with other drug users and often by buying and selling cannabis and other illicit drugs to finance their own drug use (5).

11.4 Summary

Research on adolescent use of cannabis and other illicit drug use has revealed a number of consistent findings about the relationship between cannabis and other illicit drug use. First, among American adolescents in the 1970s the use of alcohol and tobacco preceded use of cannabis, which in turn, preceded the use of hallucinogens and 'pills', and the use of heroin and cocaine. Generally, the earlier the age of initiation into drug 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 sequence. Similar sequences have been observed in a variety of societies, including Australia.

The explanation of the role of cannabis in the sequence of illicit drug use remains controversial. The relationship does not appear to be spurious. The hypothesis that the sequence of drug use represents a direct pharmacological effect of cannabis use upon the

use of later drugs in the sequence is not compelling. It also seems unlikely that the association between regular cannabis use and the use of other illicit drugs is *wholly* the result of shared risk factors or common causes. Selective recruitment of socially deviant adolescents to cannabis use, plays some role but it also does not explain the relationship. A shared genetic vulnerability to alcohol, tobacco and cannabis dependence is a plausible explanation that cannot be excluded on the available evidence.

If there is a causal relationship between cannabis and other illicit drug use the explanation is more likely to be a sociological than a pharmacological one. The fact that cannabis use predicts an increased chance of using other illicit drugs reflects a combination of: (1) the selective recruitment to heavy cannabis use of persons with pre-existing personality and attitudinal traits (possibly genetic in origin) that predispose to the use of other intoxicants; (2) their affiliation with drug using peers; (3) socialisation into an illicit drug subculture in which there is an increased opportunity and encouragement to use other illicit drugs; (4) increased access to opportunities to purchase and use other illicit drugs because of involvement in illicit drug markets as buyers and sellers; and possibly (5) a shared genetic vulnerability to use and become dependent on a range of different drugs.

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12 Effects on adolescent psychosocial development

There have been two dominant concerns about the effects of adolescent cannabis use on psychosocial development. One is that adolescent cannabis use may adversely affect educational outcomes. The other is that cannabis use may adversely affect other psychosocial outcomes, such as employment, involvement in crime, and mental health. The evidence relevant to these concerns is discussed in this chapter.

12.1 Adolescent cannabis use and educational performance

It is reasonable to suspect that adolescent cannabis use may impair educational performance and increase the chances that a student will discontinue their education (1). Cannabis use acutely impairs memory and attention and, if used regularly, it could impair learning and school performance, thereby increasing the chance of a student dropping out of school. If the adolescent's school performance was marginal to begin with, as research suggests it is among regular cannabis users, then cannabis use could increase the risk of school failure. Since high school education is so important to occupational choice, this potential effect of adolescent cannabis use could flow through the individual's life.

A number of cross-sectional surveys have examined relationships between cannabis use and educational attainment among school children and youth. The measures of educational outcome have only rarely included school grades and examination performances. Instead these studies have measured truancy and early school leaving, perhaps because confidentiality and privacy preclude access to school grades and performance in external examinations.

Resnick et al (2) reported that a low grade point average was associated with cannabis use in a national sample of 12,118 adolescents in the USA. Brook et al (3) reported that among 1,687 Colombian adolescents those who were dissatisfied with school were more likely to use cannabis. In an Australian study of 199 high school students aged 13–16 years, Jones and Heaven found that young people who were regular cannabis users had a more negative attitude toward school and a poorer record of school attendance than those who were not (4). Lifrak et al reported a negative correlation between cannabis use and scholastic competence for boys (but not for girls) in a sample of 271 seventh and eight grade students (5). Novins & Mitchell (6) also reported a significant association between poor school performance and cannabis use for males (but not females) in a sample of 1464 Native American adolescents.

A number of studies have shown that rates of cannabis and other illicit drug use are higher among young people who either no longer attend school or who are absent from school on any given day. For example, Lynskey et al (7) found that young people in the

Australian School Students' Alcohol and Drugs Survey who reported being away from school the day before the survey had higher rates of cannabis use than students who attended school on that day. Similarly, Fergusson, Lynskey and Horwood (8) found that truancy was more common among cannabis users in a sample of nearly 1,000 16 year old New Zealanders.

Mensch and Kandel (9) examined relationships between educational achievement and cannabis use in the US National Longitudinal Survey of Young Adults. They found that high school graduates reported significantly more cannabis use during adolescence than college graduates, even after controlling for socio-demographic factors, and differences in academic ability, self-esteem and delinquency. The value of this study was compromised by a reliance on retrospective reports of cannabis use, the reliability and validity of which have been questioned (10).

12.2 Explaining the relationship

Four broad explanations of the relationship between cannabis use and educational outcome need to be considered. The first and simplest explanation of the association is that early cannabis use causes poor educational outcomes. Kandel, Davies, Karus and Yamaguchi (11) argued that early cannabis use encourages continued use of the drug, and that cannabis and other illicit drug use encourages anti-conventional behaviours including early school leaving, delinquency, employment problems and difficulties in interpersonal relationships.

A second alternative explanation is that heavy cannabis use is a *consequence* of poor educational attainment. There is some support for this hypothesis in that poor educational performance is a risk factor that precedes cannabis use (12–16). The hypotheses that cannabis use is a cause of poor school performance and that poor school performance is a cause of cannabis use are not mutually exclusive. Both processes could be at work (17) if poor school performance increased the risks of using cannabis, which in turn worsened school performance.

A third possible explanation is that cannabis use and poor educational attainment are reflections of a common syndrome of problem behaviour (18). A wide range of problem behaviours in adolescence are manifestations of a common syndrome of problem behaviours (19).

The final possibility is that the associations between early cannabis use and poor educational outcomes are not causal but the result of common factors that increase the likelihood of both early cannabis use and poor educational performance. There is evidence that the risk factors and life pathways for early cannabis use overlap considerably with those for poor educational performance. These risk factors (see reviews by (15, 20, 21) include: the extent to which the norms and attitudes of the wider community encourage or discourage the use of drugs; social disadvantage and family dysfunction; individual factors including personality and an individual's propensity to violate norms; and the extent to which an individual affiliates with delinquent and drug using peers.

12.3 Longitudinal studies of cannabis use and educational outcomes

These four explanations can only be distinguished by prospective longitudinal studies in which a large representative group of young people is assessed over time on their cannabis use, educational attainment and other potentially confounding factors, such as family and social circumstances, personality characteristics and delinquency. These studies have the following strengths (22). First, they enable us to tell which comes first, cannabis use or poor educational performance. Second, they reduce the effects of bias in retrospective reports of cannabis use and behaviour. Third, they enable us to test causal hypotheses about cannabis use and educational outcomes by statistically adjusting for confounding variables. That is, they allow us to answer the question: do young people who use cannabis have poorer educational outcomes than those who do not, when we allow for the fact that cannabis users are more likely to perform poorly in school before they used cannabis?

Newcomb and Bentler (23) followed a sample of 654 high school students over 8 years to assess the impact of early substance use on educational outcomes at ages 19 to 24 years. They used statistical methods to examine the extent to which cannabis and other drug use were associated with adverse outcomes in young adulthood, after taking account of the effects of confounding factors. Their analyses indicated that early substance users were more likely to abandon a college education.

The results of this study have been supported by Fergusson, Lynskey and Horwood (24) who examined the extent to which cannabis use before the age of 15 years predicted regular drug use, criminal offending, poor mental health and reduced life opportunities at age 16, after adjusting for a range of potentially confounding factors. The sample consisted of 990 young people who had been followed from birth to age 16 years. They were assessed on cannabis use at age 15 and on cannabis use and a wide range of other health and psychological outcomes at age 16.

The ten percent of the sample who had used cannabis by the age of 15 had elevated risks of school problems at age 16. Specifically, 22.5% had left school before age 16 (the minimum school leaving age in New Zealand) compared with only 3.5% of those who had not used cannabis. The frequency of truancy between 15 and 16 years was also higher among those who had used cannabis before the age of 15 years (31.5%) than those who had not used cannabis (4.7%). The relationship between early cannabis use and early school leaving persisted after statistical adjustment for pre-existing differences between early cannabis users and their peers. In a later follow-up of the same birth cohort, Fergusson and Horwood (25) reported that those who had used cannabis before the age of 16 years were more likely to leave school without formal qualifications. This relationship also persisted after control for a wide range of confounding variables.

Duncan et al (12) examined the factors that predicted escalation of substance use in 664 adolescents who were assessed at three time points. They found that academic failure predicted higher levels of substance use (including cannabis use) at the initial time period. Deteriorating academic performance over the course of the study was also associated with increasing substance use.

Ellickson et al assessed cannabis use and a range of other factors in seventh graders who were followed up five years later (26). Cannabis use predicted early school leaving among Latino students, even after controlling for demographic variables, family structure, academic orientation and early deviance. Young Latinos who were heavy cannabis users were more likely to leave school before graduating. After controlling for these confounding factors, cannabis use did not predict early school leaving for Asians, Blacks or Whites.

Garnier, Stein and Jacobs (27) conducted a long-term prospective study of early high school drop-out. They reported that early school leaving was determined by multiple factors, which included adolescent drug use. They found that, after taking account of a range of other determinants of early school leaving, there was still a significant association between drug use assessed at age 17 years and early school leaving.

Krohn, Lizotte and Perez (17) reported that the use of alcohol and other drugs during adolescence increased the risks of precocious transitions to a range of adult roles, including leaving school early. They used longitudinal data from a sample of 775 high-risk adolescents studied from age 13 to 20 years. Early substance use, measured by frequency of alcohol, cannabis and other illicit drug use, predicted early school leaving for males but not for females.

Tanner, Davies and O'Grady (28) used data from the National Longitudinal Study of Youth to examine the influence of drug use (assessed between 14 and 17 years) on social outcomes assessed between the ages of 25 to 30 years. These included educational outcomes (highest grade completed, graduation from high school, college degree) and employment variables (occupational status, unemployment). They found that (after controlling for socio-demographic background, cognitive skill and educational expectations) early drug use predicted early school drop out, failure to graduate from high school and failure to obtain a college degree in males and females. Among males early drug use was also related to lower occupational status and unemployment.

Similar findings have been reported by Brook, Balka and Whiteman (29) in a sample of 1182 Puerto Rican and African American students who were followed over a five year period. Young people who reported using cannabis once a month or more often at age 14 were more likely to leave high school before completing 12th grade, even after controlling for a range of factors assessed at age 14. Young people who used cannabis at least monthly at age 14 were also more likely to report delinquency, other drug related problems, sexual risk taking and to have more friends who exhibited deviant behaviour.

In summary, a number of longitudinal research studies have generally shown that early cannabis use is a risk factor for poor educational outcomes and, in particular, early school leaving. A causal interpretation of the link between early cannabis use and subsequent educational performance has been supported by the fact that many of these studies have statistically controlled for a wide range of variables on which cannabis users and non-users differ. In these studies early cannabis use predicts an increased risk of early school leaving and making precocious transitions to adult roles by: engaging in early sexual activity (30), unplanned pregnancy during adolescence (17, 31), unemployment (25), and leaving the family home (17).

12.4 Explaining the association between cannabis use and early school leaving

In the better longitudinal studies statistical methods have taken account of a wide range of potential explanations of the association between cannabis use and early school leaving. Perhaps the most comprehensive effort was the study by Fergusson et al (24). Their results, and those of other studies, indicate that, even though statistical control substantially reduces the associations between cannabis use and early school leaving, a significant association remains.

It is still possible that the association between cannabis use and early school leaving arises from the effects of factors that were not measured in the studies, such as neighbourhood effects (32) and genetic vulnerability (33). The difficulty in making a causal inference is not peculiar to the relationship between cannabis use and early school leaving. A number of studies, for example, have found a relationship between cigarette smoking and early school leaving which remains after extensive statistical control for confounding factors (25, 26). There is no obvious biological explanation of the relationship so it is more likely to reflect uncontrolled factors that are associated with tobacco use and early school leaving. Although a similar possibility cannot be excluded with respect to cannabis, a number of explanations have been suggested of the relationship between cannabis use and early school leaving.

12.5 Does cannabis use produce an 'amotivational' syndrome?

Daily cannabis use over months and years has been reported to impair motivation and social performance in users in Egypt and the Caribbean (34) (see chapter 6). The existence of an 'amotivational syndrome' among chronic heavy cannabis users has not been supported by the results of a number of field studies conducted in societies where heavy cannabis use is widespread, including Jamaica (35) and Costa Rica (36) (see chapter 6). Evidence reviewed in chapter 6 suggests that an amotivational syndrome is rare, if it exists (37, 38) and 'it may be more parsimonious to regard impaired motivation as a symptom of chronic cannabis intoxication' (p.277) (39). Hence, it appears unlikely that 'amotivation' explains poor school performance.

12.6 Does cannabis use produce cognitive deficits?

A third explanation is that cannabis use causes cognitive impairment, which increases the likelihood of leaving school early. The evidence (as reviewed in chapter 8) indicates that long-term cannabis use does not produce marked impairments in thinking and memory that are as easily detected as those found in long-term heavy alcohol consumers (40). Solowij has argued that daily or near cannabis use over periods of three or more years does produce subtle impairment in selective attention in adults.

These deficits are of doubtful relevance to adolescent cannabis users because few would have used cannabis intensively or long enough to produce the effects found in adults.

The adults in the studies reviewed by Solowij, for example, used cannabis daily for an average of 10 years. By contrast, in the study reported by Fergusson and Horwood (25) the 'heavy' cannabis use group included those who had smoked cannabis on at least ten occasions. There is no evidence in the scientific literature on adults that such low levels of use are associated with any lasting cognitive impairment.

This does not mean that acute cognitive impairment is irrelevant in adolescents. Rather it suggests that any cognitive impairment in cannabis using adolescents is more likely to result from the *acute* effects of cannabis use rather than the effects of long-term use. If cannabis intoxication became an everyday occurrence in the life of an adolescent, their school performance would suffer, especially if it was poor to begin with.

12.7 Does early cannabis use lead to the precocious adoption of adult roles?

Fergusson and Horwood (25) have argued that the effects of early adolescent cannabis use on later development can be attributed to the social setting in which adolescents use cannabis, namely within a group of delinquent and substance using peers. Their views are in agreement with those of Kandel et al (11) who argued that early substance use sets in train a cascade of events that increases later psychosocial risk. On Fergusson and Horwood (25)'s hypothesis, the important causal factors is that cannabis use occurs in a peer group that rejects conventional values, such as high educational achievement and social conformity, and which instead encourages non-conformist behaviour and a premature transition to adulthood.

12.8 Other effects of adolescent cannabis use

12.8.1 Occupational performance

Among young cannabis users who enter the work-force the continued use of cannabis and other illicit drugs in young adulthood might impair job performance for the same reasons that it may impair school performance, namely, that chronic intoxication impairs cognitive and psychomotor performance. There is some support for this expectation in that cannabis users report higher rates of unemployment than nonusers (e.g. (41, 42) but this comparison is confounded by the different educational qualifications of the two groups.

Mensch and Kandel (9) examined cross-sectional relationships between alcohol, tobacco and cannabis use and performance in a range of occupations in a nationally representative sample of Americans. Apart from tobacco use there were only modest associations between cannabis use and occupation. There were very weak negative correlations between job satisfaction and tobacco smoking and cannabis use. Workers in occupations that were lacking in 'complexity, intellectual flexibility and variety' were more likely to smoke cannabis at work, perhaps because heavier cannabis users seek or are forced to accept less challenging jobs. Cannabis use and tobacco smoking were associated with 'lack of conformity or attachment to social institutions, such as having dropped out of school, having participated in delinquent activities, or not being married' (p 181).